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SARCOIDOSIS

VASCULITIS AND DIFFUSE LUNG DISEASES

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SARCOIDOSIS

VASCULITIS AND DIFFUSE LUNG DISEASES

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ITS – AIPO - Associazione Italiana Pneumologi Ospedalieri
Via Antonio da Recanate, 2
20124 Milano
Tel. +39 02 36590367
Fax +39 02 67382337
www.aiponet.it
aiposegreteria@aiporicerche.it

Società Italiana Di Pneumologia / Italian Respiratory Society (SIP/IRS)
Via San Gregorio, 12
20124 – Milano – Italy
Tel. +39 0249453331
Fax + 39 0287036090
mail segreteria@sipirs.it
web www.sipirs.it

PUBLISHER
Mattioli 1885 - Strada di Lodesana 649/sx, Loc. Vaio - 43036 Fidenza (Parma)
Tel. +39 0524 530383 - Fax +39 0524 82537 - www.mattiolihealth.com - edit@mattioli1885.com

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Sarcoidosis Vasculitis and Diffuse Lung Disease: alive and still growing

In 2004, the journal Sarcoidosis was launched by Professor Gianfranco Rizzato. With the support of Drs. D. Geraint James, Carlo Agostini, and Gianpietro Semenzato, the journal quickly became the leading source of new information regarding sarcoidosis. When the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) was formed, the journal became its official journal.

In 2008, Dr. Rizzato step down from his role as Chief Editor. Drs. Cesare Saltini and Robert Baughman became co-chief editors and two years later were joined by Venerino Poletti.

Over the past twelve years, there have been significant changes in the journal. The journal's cost of publication was mainly supported by the Italian societies AIPO Associazione Italiana Pneumologi Ospedalieri, Italia and Società Italiana di Pneumologia / Italian Respiratory Society (SIP/IRS). Because of production costs, the journal became an on-line journal. The most significant change was that in 2018, when articles published in the journal were not listed in PubMED.

After tireless work of our new Chief Editorial team and Valeria Ceci, we are pleased to announce that we have been reinstated on PubMED. Articles published during the past two years have now been added to PubMED.

In addition, the journal has been able to keep its commitment to make all articles immediately available for down loading. Open access to the articles can be obtained by visiting the journals website at https://www.mattioli1885journals.com/index.php/sarcoidosis/issue/view/712.

There is much that still needs to be done. We need more articles and we need more reviewers. Those of you who have provided reviews over the past few years, we thank you. For those unable to review in the past, please consider helping to keep the journal going.

We encourage you to read the journal and cite articles in your own work. The journal has an important legacy in sarcoidosis. Please help us maintain the standards that Dr. Rizzato established when he launched the journal in 1984.

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Infection prevention in sarcoidosis: proposal for vaccination and prophylactic therapy

Huzaefah Syed[1], Christian Ascoli[2], Catharina FM Linssen[3], Christen Vagts[2], Thomas Iden[4], Aamer Syed[4], Jordana Kron[5], Kelly Polly[4], David Perkins[6], Patricia W Finn[2], Richard Novak[7], Marjolein Drent[8,9], Robert Baughman[10], Nadera J Sweiss[2,11]

[1] Division of Rheumatology, Allergy, and Immunology, Virginia Commonwealth University, Richmond, VA, USA; [2] Division of Pulmonary, Critical Care, Sleep, and Allergy, University of Illinois at Chicago, Chicago, IL, USA; [3] Department of Medical Microbiology, Zuyderland Medical Centre, Heerlen/Sittard-Geleen, the Netherlands; [4] Division of Pulmonary and Critical Care, Virginia Commonwealth University, Richmond, VA, USA; [5] Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA; [6] Division of Nephrology, University of Illinois at Chicago, Chicago, IL, USA. ; [7] Division of Infectious Diseases, University of Illinois at Chicago, Chicago, IL, USA; [8] ILD Center of Excellence, St. Antonius Hospital, Nieuwegein, The Netherlands; [9] Department of Pharmacology and Toxicology, FHML, Maastricht University, Maastricht, The Netherlands; [10] Department of Internal Medicine, University of Cincinnati Medical Center, Cincinnati, OH, USA; [11] Division of Rheumatology, University of Illinois at Chicago, Chicago, IL, USA

Abstract. Sarcoidosis is a systemic inflammatory disease characterized by granuloma formation in affected organs and caused by dysregulated immune response to an unknown antigen. Sarcoidosis patients receiving immunosuppressive medications are at increased risk of infection. Lymphopenia is also commonly seen among patient with sarcoidosis. In this review, risk of infections, including opportunistic infections, will be outlined. Recommendations for vaccinations and prophylactic therapy based on literature review will also be summarized. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 87-98).*

Key words: Sarcoidosis, infections, opportunistic infections, vaccinations, immunizations, prophylaxis, travel

Key points: Infections are common is patients with sarcoidosis receiving immunosuppressive therapy; Current guidelines for infection prevention and vaccination in sarcoidosis patients are lacking; Personalized approach is required when prescribing immunosuprresive therapy to sarcoidosis patients taking into consideration risk of infection and proper vaccination.

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Correspondence: Huzaefah Syed, MD, MPH
Division of Rheumatology, Allergy, and Immunology Department of Internal Medicine Virginia Commonwealth University
1112 E. Clay Street, Suite 1-110
PO Box 980623 Richmond, VA 23225
E-mail: Huzaefah.syed@vcuhealth.org

Introduction

Sarcoidosis is a systemic disorder that develops in response to an unknown antigen and is typically characterized by a heightened local inflammatory reaction characterized by granuloma formation and cytokine secretion in affected organs. Patients with sarcoidosis have been noted to have an increased risk of infection requiring hospitalization, especially pneumonia and some opportunistic infections[1,2,3]. Although not fully elucidated, several mechanisms inherent to sarcoidosis and likely a result of the complex dysregulated immune response observed in

sarcoidosis (such as peripheral anergy as well as loss of local defenses when bronchiectasis and cavitations develop), contribute to this increased infectious susceptibility [1,2,3]. Clinically significant peripheral lymphopenia and hypogammaglobulinemia are usually seen in association with immunosuppressive therapy, including corticosteroids. Additionally, patients with symptomatic disease are frequently treated with immunosuppressive medications which further disrupts inherent immunologic mechanisms.

As with other inflammatory diseases, on account of the immunosuppressive effects of the disease itself and the use of immunosuppressive medications, it is important to prevent infectious diseases and associated complications in sarcoidosis patients. Vaccination is generally regarded as a safe, efficacious and low-cost method that may reduce morbidity and mortality associated with sarcoidosis patients and prophylactic therapies may further be a safe and cost-effective manner of prevention[4,5,6]. It is therefore imperative to ensure patients are properly vaccinated and placed on prophylactic therapy when indicated to prevent infections. However, it has been observed that lack of physician rescommendation to do so is a predominant factor to the low rates of vaccination among immunosuppressed patients[7]. Specifically in sarcoidosis, and further contributing to low rates of vaccination and prophylaxis, we recognize that currently there are no guidelines on immunization or prophylaxis practices. Although data cannot be clearly extrapolated from other diseases, the recommendations for patients with autoimmune diseases and some forms of immunosuppression are likely applicable to sarcoidosis patients. In this review, we will outline the risk of infection in patients with sarcoidosis and immunosuppressive medications and recommendations for vaccinations and prophylactic therapy for sarcoidosis patients will be proposed.

Immunosuppressive Therapy and Infection Risk

Oral immunosuppressants commonly used in sarcoidosis

Of the oral immunosuppressant medications, glucocorticoids are found to be the highest risk for the development of infection. In a study done by Bernatsky, the relative risk of infections requiring hospitalization in those taking glucocorticoids was 2.56 (95% CI 2.29-2.85)[8]. Another study showed the relative risk of infections from glucocorticoids was 1.6 (95% CI 1.3-1.9), and the rates of infection increased with higher doses[9]. However, patients taking less than 10mg of prednisone daily (or its equivalent) did not have higher infection rates compared to those not taking glucocorticoids[10]. Furthermore, risk of infection increased in patients taking combination therapy, either glucocorticoids plus a steroid-sparing agent or more than one steroid-sparing agent together.

Methotrexate can cause cytopenias in about 5.2% of patients, which can, in part, predispose patients to infections[11]. However, a Cochrane review by Lopez-Olivo et al shows that the relative risk of serious adverse events in patients treated with methotrexate as compared to placebo is 1.44 (95% CI 0.36-5.74) and the relative risk of infection is 1.26 (95% CI 1.01-1.57)[12]. A systematic review by Salliot et al showed that of patients who were on methotrexate for rheumatoid arthritis (RA) over a three year period, 8.3% developed infections[11].

Azathioprine, a purine analog, is converted to 6-mercaptopurine, then further degraded into its nontoxic metabolites by thiopurine methlytransferase. Azathioprine may cause myelosuppression, increasing its infectious risk profile. Those patients with a deficiency in thiopurine methyltransferase are at increased risk of azathioprine toxicity and lower doses of azathioprine should be used or avoided completely, and cell counts closely monitored[13]. A Cochran Review by Suarez-Alamazor et al shows the odds ratio of developing cytopenias with azathioprine as compared to placebo was 6.84 (95% CI 0.69-68.05)[14]. In a study completed by Bernatsky, the relative risk of infections requiring hospitalizations in patients taking azathioprine compared to placebo was 1.52 (95% CI 1.18-1.97) [8].

Other oral disease modifying anti-sarcoid drugs (DMASD) are commonly used off-lable in sarcoidosis patients. However the risk of significant immunosuppression with these agents is unknown[15].

Significant immunosuppression with oral agents is considered to occur with > 2 weeks of prednisolone > 10mg/day (or its equivalent), methotrexate ≥ 0.4mg/kg/week, and azathioprine ≥ 3mg/kg/day[7].

Biologic Therapy Commonly Used in Sarcoidosis

Biologic therapy carries an increased risk of numerous types of infections. In a study conducted

on 3,111 veteran patients with rheumatoid arthritis (RA), who had 4,158 treatment episodes with a biologic (defined as new biologic treatment, either abatacept, rituximab, or an anti-TNF agent), pneumonia was seen in 37%, cellulitis in 22%, urinary tract infections in 9% and bacteremia or sepsis in 7%. Hospitalized infection rates per 100 years were 4.4 (95% CI 3.1-6.4) for rituximab and 3.0 (95% CI 2.5-3.5) for anti-TNF agents[16]. In a study evaluating efficacy and safety of anti-TNF agents in sarcoidosis patients, Jamilloux et al found an infection rate of 36% among 132 patients[17]. In a systematic review and meta-analysis of small molecule JAK kinase inhibitors in RA patients, the incidence rate of serious infections among 5,888 patients taking tofacitinib 5mg twice daily was 1.97 (95% CI 1.41-2.68), and the incidence rate ratio when comparing to the placebo arm was 1.22 (95% CI 0.60-2.45) [18].

Infection risk may also depend on dose of biologic therapy. A meta-analysis conducted by Leombruno et al reviewed 18 randomized trials with a total of 8808 patients with RA who were either randomized to anti-TNF agents (further divided into recommended dose vs high dose therapy), conventional synthetic disease modifying anti-rheumatic drugs (DMARDs), or placebo. High dose therapy was defined as the following: adalimumab > 40mg every 2 weeks, etanercept > 50mg weekly, and infliximab > 8mg/kg every 8 weeks. Over an average follow-up of 0.8 years, the authors did not find a statistically significant increase in infections in the synthetic DMARDs or placebo group compared to the recommended dose anti-TNF group. However, the high dose anti-TNF group had a two-fold increased risk of infections[19]. This is of particular importance in sarcoidosis, as high dose therapy is often used, in the absence of prospective randomized data. Another systematicic review and meta-analysis of anti-TNF use assessed the risk of infection in RA patients who were given standard dose anti-TNFs, high dose anti-TNFs, or control therapy. High dose anti-TNFs were defined as infliximab > 3mg/kg every 8 weeks and adalimumab > 40mg every other week. The authors found an OR of 2.3 (95% CI, 1.5-3.6) for the high-dose anti-TNF group compared to the control group and an OR of 1.8 (95% CI, 1.1-3.1) for the standard-dose group compared to the control group. However, when comparing the high-dose group to the standard-dose group, an OR of 1.4 was not found to be statistically significant (95% CI, 1.0-2.0, P = 0.07)[20].

Adelzadeh et al completed a meta-analysis that evaluated the risk of herpes zoster in patients taking different biologic therapy (infliximab, adalimumab, etanercept, and ustekinumab) and found slightly higher rates of zosters in patients taking infliximab. Data for the other biologics showed varying rates, making the results inconclusive[21]. In the aforementioned systematic review and meta-analysis evaluating infection risk with tofacitinib, the incidence rate for developing herpes zoster was 2.51 (95% CI 1.87-3.30), but the incidence ratio rate when comparing to the placebo arm was no longer significant (1.38 with 95% CI 0.66-2.88)[18]. In a retrospective review of Medicare patients with RA, older patients tended to be at high risk of developing zoster regardless of biologic used, but the highest adjusted hazard ratio was seen among patients taking oral corticosteroids (> 7.5mg daily of prednisone or its equivalent)[22].

Rituximab is also associated with increased infections, with serious infections encountered at rate of 3.76 per 100 patient years, although not all analyses reported an increased risk[23,24,25,26]. Because of its suppression of immunoglobulin production, there is an overall increased risk for viral infections. Rituximab has been shown to cause reactivation of herpes simplex virus, herpes zoster virus, and hepatitis B[27,28]. However, prolonged use of rituximab can lead to IgG depletion and neutropenia, and monitoring IgG levels on a regular basis is recommended. Immunoglobulin replacement therapy can be effective in reducing risk of infections in patients on prolonged rituximab therapy, but there are currently no guidelines on when and in which patients this should be done[29,30,31,32,33,34,35].

Infections in Sarcoidosis

In sarcoidosis patients specifically, various infections have been described while on immunosuppressive therapies. Dureault et al examined infection rates in 585 patients, and reported 22 episodes of severe non-mycobacterial infections among 16 patients, and 14 mycobacterial infections among 14 patients[2]. Patients with severe infections were more likely to have been treated with ≥ 3 immunosuppressive agents. Although limited, current data suggests patients with sarcoidosis are at increased risk of infection regardless of immunosuppressant therapy. A retrospective review by Ungprasert et al found that patients with sarcoidosis had an increased incidence of community acquired infection requiring

hospitalization compared to age- and sex-matched healthy controls (HR 2.00, 95% CI 1.14-2.84). Less than half of this cohort was on immunosuppressive therapy. Risk factors for infections included baseline diffusing capacity of the lung for carbon monoxide (DLCO) and baseline forced vital capacity (FVC), with a steady increase in infection rates with decreases in DLCO and FVC[1]. Further study is needed to further delineate infection risk in treatment-naïve sarcoid.

Opportunistic infections

Due to inherent and medication-induced immunosuppression, sarcoidosis patients have been shown to be at increased risk for opportunistic infections, albeit infrequently. Reported infections include *Pneumocystis jirovecii* pneumonia (PJP), Mycobacterial infection, *Cryptococcus neoformans* , and aspergillosis. Epidemiologic and geographic factors, as well as presence of parenchymal fibrosis, also play a part. Opportunistic infections have been observed in other autoimmune diseases in conjuncture with initiation of immunosuppressive medications. A large retrospective review identified opportunistic infections at an incidence rate of 0.045% , among patients who were newly started on either biologic or immunosuppressive therapy. Of the patients newly started on biologic therapy, the most commonly occurring infections were PJP (20%), nocardiosis (15%), tuberculosis (12.5%), histoplasmosis and non-tuberculosis mycobacteria (11.3% each), and salmonellosis (10%). The other opportunistic infections reported occurred in ≤ 5% of the cases[36].

PJP is a commonly known opportunistic infection that affects HIV-positive patients as well as non-HIV, immunocompromised patients. In those without HIV, it tends to have a more severe course with rapidly progressive and fatal disease[37]. Several studies have reported the prevalence of PJP among patients with autoimmune disease to range from 0.18% to 1.2%, with the highest risk being among those on corticosteroid therapy, especially at doses > 20mg/day[38,39,40,41,42]. Other risk factors include older age and co-existing pulmonary disease[40]. PJP has been infrequently reported in sarcoidosis.

Mycobacterial infection has not often been reported in patients with sarcoidosis. As mycobacterial infection, especially tuberculosis, can present as granulomatous disease, it should be on the differential when assessing for sarcoidosis. There have been 27 reported cases of tuberculosis among sarcoidosis patients between 1976 and 2013, of which 74% were in patients being treated with corticosteroids.[43]. Fourteen non-tuberculosis mycobacterium cases were reported between 1977 and 2010, of which 71% were receiving corticosteroid therapy. A greater risk for tuberculosis than sarcoidosis itself is TNF-alpha inhibitors, which are frequently used to treat sarcoidosis. This increased risk has been observed more commonly with infliximab and adalimumab than with etanercept[44,45,46]. Furthermore, TNF-alpha has been shown to play a part in the host defense against tuberculosis, and blockade of TNF-alpha can lead to reactivation of latent tuberculosis. A meta-analysis of 29 randomized clinical trials evaluating incidence of tuberculosis in patients on anti-TNF therapy identified 45 patients (0.57%) on anti-TNF therapy who developed tuberculosis, compared to only 3 of 3967 control patients who developed tuberculosis ($p = 0.02$)[47]. A systematic review of 40 randomized controlled trials with a total of 14,683 patients found an odds ratio of 24.8 for developing TB while on anti-TNF therapy (95% CI 2.4-133). When anti-TNF agents were combined with other immunosuppressive agents (methotrexate or azathioprine), the odds ratio increased to 54 (95% CI 5.3-88)[48].

Fungal infections in patients with sarcoidosis has been sparsely reported. Baughman's study found 7 cases of fungal infection among 753 cases of sarcoidosis[49]. CrytpOsarc, a study completed by Bernard et al, identified 18 patients with cryptococcal infection and sarcoidosis and found that sarcoidosis accounted for 2.6% of the non-HIV associated cryptococcal infections[50]. One third of the identified patients were not on corticosteroids at the time of diagnosed infection, though presence of other immunosuppressants is not mentioned. Increased rates of aspergillosis have been documented among patients with chronic pulmonary fibrotic disease, and have been noted to occur more frequently in sarcoidosis than in other interstitial lung diseases[3]. Again, corticosteroids play an important role as a risk factor for development of aspergillosis as does mold exposure[2].

Progressive multifocal leukoencephalopathy (PML) is more likely to occur in immunocompromised patients but has been reported in sarcoidosis

patients not on immunosuppression. There are case reports of symptoms and magnetic resonance imaging (MRI) findings mistakenly attributed to neurosarcoidosis, leading to increased immunosuppression and worsening of symptoms[17,51,52]. The presentation of sarcoidosis-associated PML differs from neurosarcoidosis. In PML, cererbospinal fluid (CSF) is typically normal and MRI brain shows multifocal asymmetrical subcortical white matter lesions that are hypointense on T1, hyperintense on T2, and non-enhancing with contrast. In neurosarcoidosis, CSF frequently has pleocytosis and elevated protein but can be normal. MRI of the brain typically shows meningeal or parenchymal lesions with contrast enhancement. Definitive diagnosis requires JC virus DNA detection in the CSF by polymerase chain reaction or brain biopsy. JC virus may not be detected in CSF in early disease so it may require repeat lumbar puncture to diagnose. Brain biopsy can be considered if suspicion remains high[17,43].

Herpes zoster is reported infrequently in patients with sarcoidosis, and likely occurs at the same rate as the general population[53,54]. There are reports of sarcoid granulomas occurring at the sites of healed zoster lesions[55,56,57].

Recommendations for Vaccinations

As described, the dysregulated immune response underlying granuloma formation in sarcoidosis along with use of immunosuppressive therapies contributes to overall immune dysfunction. Despite the infection risk, there are no current guidelines on immunization practices in sarcoidosis patients. Although data describing infection risk in sarcoidosis is lacking, the recommendations for vaccinations in immunosuppressed patients are likely applicable to sarcoidosis patients. As sarcoidososis most commonly affects the lungs, vaccination should be considered in alignment with recommendations for chronic lung disease. Special consideration for vaccination should be taken in regards to use of immunosuppressive therapy and type of vaccine. Discussion with patients should also include possibly vaccinating household members and those who are regularly in close contact with the patient.

All new patients should be screened for their vaccination status and administer any appropriate immunizations prior to the start of immunosuppressive therapy[7]. Though patients with immune-mediated disease have been shown to have a comparable serologic response to vaccinations as those in the general population, immunosuppressive therapy can interfere with the immune response. This is most concerning with biologic therapy, especially rituximab, a B cell depletion therapy [58]. Patients treated with rituximab have been shown to have lower probability of immune response to various vaccines and absent antibody titers to influenza vaccines and pneumococcal vaccines[58,59,60]. In order to allow an adequate immune response, it would be best to wait two weeks after vaccinations to start immunosuppressive therapy[7]. If a patient is already receiving immunosuppressive therapy, therapy need not be held to administer inactivated vaccines. Though immunogenicity may be lower, there is still a protective response from the vaccinations.

However, when considering live vaccinations for patients on immunosuppressive medications, there should be careful thought to ensure benefits outweigh the risks. If possible, immunosuppressive therapy should be held 2-4 weeks prior to the administration of live vaccines, and the length of viremia should help determine when to restart immunosuppressive therapy. Special consideration should be given to patients receiving live vaccines while on rituximab; vaccinations should not be given until at least 5 months after the last dose of rituximab, and rituximab should not be re-dosed for at least one month after vaccinations[7].

Table 1 summarizes the list of vaccinations and Table 2 proposes the use of these vaccinations in patients with sarcoidosis.

Influenza

In sarcoidosis, as is the case with many other diseases, the presence of chronic pulmonary disease and impaired immune function likely predisposes to higher risk of complications, increased severity of disease and death from influenza[61]. The protective effect rendered by vaccination with modern influenza vaccines results from induction of antibody production against hemagglutinin (HA) or neuroaminidase antigens[62].

Currently, the CDC recommends that any person 6 months of age or older should receive an influenza vaccination unless contraindicated because of severe allergy or other special considerations (e.g.:

Table 1. Recommendations for vaccinations in immunosuppressed patients.

Vaccination	Age	Frequency	Special Considerations
Influenza, inactivated or recombinant	6 months an older	Annually	
Pneumococcal PCV13 (Prevnar) PPSV23 (Pneumovax)	≥ 19 years	 Once See Figure 1	 To be given no sooner than 1 year after PPSV23 To be given no sooner than 8 weeks after PCV13
Zoster (recombinant)	≥ 50 years	2 doses 2-6 month apart	
HPV	11-26 years (women) 11-21 years (men)	3 doses at months 0, 1-2, and 6	
HepA 2 dose series HepA 3 dose series HepA/B		 2 doses 6-18 months apart 3 doses at 0, 1, and 6 months	Risk factors for HepA: • chronic liver disease • clotting factor disorders • men who have sex with men • drug use (including non-injection) • homelessness • working with hepatitis A in research labs • close interaction with international adoptee within 60 days of arrival • travel to country with endemic rates
HepB 2 dose HepB 3 dose HepB 3 dose HepA/B		 2 doses > 4 weeks apart 3 doses at 1, 2, and 6 months 3 doses at 1, 2, and 6 months	Risk factors for HepB: • hepC Infection • chronic liver disease • infection with HIV • sexual exposure risk • current or recent injection drug use • percutaneous or mucosal risk of exposure to blood (including dialysis patients) • travel to country with endemic rates
Tdap If received childhood series If did not receive childhood series		 Every 10 years 3 doses at 0, 1 and 6-12 months, then every 10 years	

PCV13 – 13-valent pneumococcal conjugate vaccine. PPSV23 – 23-valent polysaccharide vaccine. HPV – human pappiloma virus. HepA – Hepatitis A. HepB – Hepatitis B. Tdap – tetanus toxoids, diphtheria, and acellular pertussis vaccine.

Table 2. Prposed use of vaccines in patients with sarcoidosis

	Killed vaccines			Live attenuated vaccine
	Pneumococcal 1	**Influenza 2**	**Hepatitis B 3**	**Herpes zoster**
Before initiating therapy				
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Recommended[4]
Non-TNF biologics	Recommended	Recommended	Recommended	Recommended[4]
While already taking therapy				
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Not recommended
Non-TNF biologics	Recommended	Recommended	Recommended	Not recommended

DMARD – disease-modifying anti-rheumatic drugs. TNFi – tumor-necrosis factor inhibitor.

patients who are unlikely to respond or who have received anti-B-cell antibodies within 6 months). Expressly, the CDC recommends that among the various types of influenza vaccines, adults 18 years of age and older receive 0.5mL of an age appropriate inactivated vaccine (trivalent or quadrivalent) or, alternatively, a recombinant quadrivalent vaccine. Notably, avoidance of live attenuated influenza vaccines in the immunocompromised individual is emphasized because of the risk of adverse events, though this is a weak recommendation with low quality of evidence[63,64]. Additionally, attention is brought to those patients 65 years of age and older given the decreased immune response to standard influenza vaccines as compared to healthy adults because of cellular senescence, and a recommendation is made which allows these individuals to receive a high-dose influenza vaccine which may provide greater immunogenicity[64,65].

In sarcoidosis, specifically, there is paucity of data evaluating the degree of susceptibility to influenza, predisposition to disease flare after administration of influenza vaccine, and the robustness of antibody production to preventative levels against influenza after vaccination. A small prospective case-control study evaluated the serological response to influenza vaccination, and found no difference in serologic response to influenza vaccines, but interestingly, patients with sarcoidosis demonstrated a higher protection rate against the influenza B antigen after vaccination. Moreover, no signs of disease flares or major adverse events were observed in the sarcoidosis group after 6 months of follow-up[66].

At the present, we recommend that immunosuppressive therapy should only be held if the risks do not risks do not outweigh the benefits. All patients without to vaccination should receive inactivated seasonal influenza vaccination yearly regardless of their therapy with a consideration for high-dose vaccination in those over 65 years of age.

Pneumococcus

Pneumococcal vaccines are typically indicated in adults over the age of 65. However, in immunocompromised patients, the CDC recommends vaccinations start at 19 years old[67].

Regardless of age, patients should receive the 13-valent pneumococcal conjugate vaccine (PCV13 or Prevnar) vaccine first followed by the 23-valent polysaccharide vaccine (PPSV23 or Pneumovax) vaccine at least eight weeks later. Patients older than 65 years old should receive each vaccine only once (PCV13 and PPSV23). Patients less than 65 years old should have up to three PPSV23 vaccines no less than 5 years apart, with only one dose being given after a patient turns 65 years old[7,67].

If the patient has already received PPSV23 first, the PCV13 should be given no sooner than one year after the PPSV23 vaccine. See Figure 1.

Tetanus, diphtheria, and pertussis (Tdap)

Tdap is typically completed as a series in childhood, and then is recommended every 10 years throughout adulthood. If a patient has not received any childhood Tdap vaccines, they should receive Tdap at 0, 1, and 6-12 months, and then a booster every 10 years[67].

Zoster

The live zoster vaccine is not recommended in anyone who is immunosuppressed. As of 2020, the CDC does not yet have a recommendation regarding recombinant zoster vaccination (Shingrix) in immunocompromised adults[68]. The recombinant vaccine is given as a two-vaccine series, 2-6 months apart. If the second vaccine in the series is given too soon, it is recommended to repeat the dose at the appropriate interval. If the second vaccine is given too late, it is recommended to start over with the two-vaccine series[7,67].

Patients who have already had a shingles infection or received the live zoster vaccine are still advised to get the recombinant zoster vaccine series[67]. Additionally, the recombinant vaccine is preferred over the live attenuated vaccine for all populations.

Hepatitis A and B

Hepatitis A (HepA) and hepatitis B (HepB) vaccines are recommended for those individuals at risk for exposure to the virus, but should also be given routinely for those who want protection. Risk factors for HepA include chronic liver disease, clotting

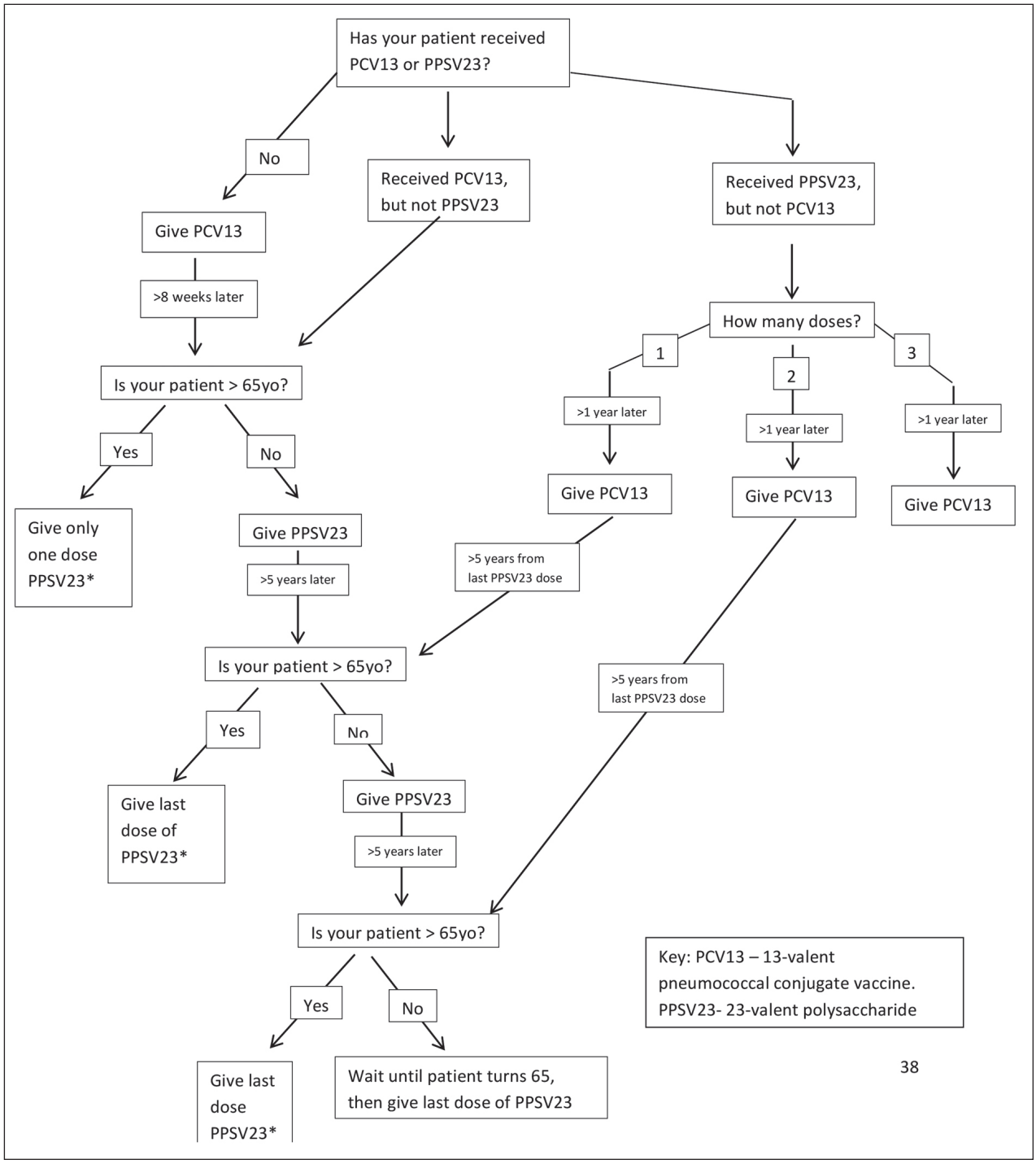

Fig. 1. Algorithm for Pneumococcal vaccine administration.

factor disorders, men who have sex with men, drug use (including non-injection), homelessness, working with hepatitis A in research labs, close interaction with international adoptee within 60 days of arrival, and travel to country with endemic rates. Risk factors for HepB include hepatitis C Infection, chronic liver disease, infection with HIV, sexual exposure risk, current or prior injection drug use, percutaneous or

mucosal risk of exposure to blood (including dialysis patients), and travel to countries with high endemic rates. Each vaccine is given as 2-3 dose series, depending on the vaccine[67].

Other vaccinations

Vaccination for Measles / Mumps / Rubella (MMR), Yellow Fever and HPV should be followed per CDC guidelines. As the MMR vaccine is typically given to patients between the ages of 12 months and 12 years old, an adult patient should be considered vaccinated if there is presumptive evidence against immunity. This evidence includes written documentation of adequate vaccination, laboratory evidence of immunity, laboratory confirmation of measles, or birth before 1957. In those without presumptive evidence against immunity, measles immunoglobulin G (IgG) levels should be obtained. If the results are negative or equivocal, then the patient should be vaccinated or re-vaccinated. If vaccination is not possible, then the patient should be sent for second line diagnostic testing at the local health department[69].

Preventive therapy for opportunistic infections:

Tuberculosis

As TNF-alpha inhibitors can lead to reactivation of latent tuberculosis, it is recommended to screen all patients for tuberculosis exposure prior to initiation of biologics. This can be done either with a tuberculin skin test (TST) or with an interferon gamma release assay (IGRA). TST studies are less sensitive but highly specific (97.6%) for the diagnosis of tuberculosis among sarcoidosis patients[70]. However, as sarcoidosis has been associated with anergy, it is difficult to say if a negative TST in a sarcoidosis patient is a true negative. Therefore, IGRA may be more helpful. In a study by Gupta et al, patients with biopsy-proven sarcoidosis, pulmonary tuberculosis, and extra-pulmonary tuberculosis, as well as healthy controls, were prospectively enrolled to receive TST and IGRA. Patients with sarcoidosis reacted to the IGRA test more frequently than the TST, and not significantly less than in healthy controls[71]. As IGRA continues to be positive in sarcoidosis patients, it may be a better diagnostic tool for tuberculosis.

In patients with a positive TST or IGRA, TNF-inhibitor therapy should only be started one month after initiation of prophylactic therapy (in cases of latent tuberculosis) or after the completion of therapy (in cases of active tuberculosis)[72]. Special consideration for anti-tuberculosis therapy should be given to patients with hepatic sarcoidosis or those on hepatoxic DMASD therapy.

Pneumocystis pneumonia (PJP)

As rates of PJP among non-HIV immunocompromised patients are low, there is no consistent data to help guide prophylaxis. . A retrospective review evaluating patients on high dose corticosteroid therapy (defined as prednisolone ≥ 30mg/day or its equivalent) with and without prophylactic therapy identified 30 cases of PJP, 29 of which were not receiving PJP prophylaxis[73]. Furthermore, a 2014 Cochrane review found a significantly reduced incidence of PJP in patients with acute leukemia or solid organ transplant who received prophylaxis by 85%. Trimethoprim-sulfamethoxazole was given thrice weekly or as a single daily dose, and the number needed to treat was 19[74]. Patients with risk factors (age older than 65 years, co-existing pulmonary disease, on corticosteroids) may benefit from prophylaxis[40]. The American Thoracic Society recommends considering prophylactic therapy for any patient who is receiving prednisone ≥ 20mg/day for ≥ 8 weeks, has an internal derangement of their immune system due to their disease, or is on a cytotoxic agent such as methotrexate or TNF-inhibitors[75]. Different regimens for prophylaxis are available (Table 3). Trimethoprim should be avoided in patients taking methotrexate as it may increase blood levels of methotrexate.

Herpes Simplex and Herpes Zoster

In patients who have a history of previous herpes simplex or zoster infection, consideration should be given for prophylactic therapy in order to prevent a flare precipitated by the initiation of DMASDs. In a Cochrane review of randomized clinical trials evaluating the efficacry of anti-virals in preventing herpes simplex infections in patients receiving cancer therapy, acyclovir was shown to be effective, with a risk ratio of 0.16 (95% CI 0.08-0.31) when

Table 3. Regimens for PJP Prophylaxis

Drug	Dosing	Comments
Dapsone	50mg BID or 100mg daily	Rule out G6PD deficiency
Dapsone/ Pyrimethamine/Leucovorin	50mg daily/50mg weekly/25mg/weekly	
Dapsone/ Pyrimethamine/Leucovorin	200mg weekly/50mg weekly/25mg/weekly	
Atovaquone (liquid)	1500mg daily	Take with food
Pentamidine (aerosolized)	300mg monthly	

compared to placebo. Further, valacyclovir was not found to be more efficacious that acyclovir[76]. According to guidelines put forth by the American Society of Clinical Oncology and the Infectious Diseases Society of America, prophylaxis with acyclovir should be considered in patients with profound neutropenia (defined as < 100 neutrophils per microliter) and seropositivity for herpes simplex[77].

Conclusion

Infection prevention and vaccination in patients with sarcoidosis are of crucial importance. There is increased risk of infection associated with the use of immunomodulatory drugs used to treat sarcoidosis. Therefore the vaccination status should be evaluated in the initial patient workup. We propose that vaccination strategies should be implemented during stable disease and reassessed perodically during regular follow up.

The immune response to various vaccines in sarcoidosis patients is not well defined. Furthermore, the effectiveness of vaccines in patients with sarcoidosis to prevent life threatening infection requires additional research. In this review, we summarized the existing literature regarding infections in sarcoidosis patients. Furthermore we propose considering vaccination in this patient population, building on the experience from patients with other autoimmune diseases

Future collaborative multi-center studies should help better understand the safety and efficacy of various vaccines in patients with sarcoidosis with and without immunomodulatory therapy. Even though the preliminary evidence is reassuring on the safety of vaccination in patients with sarcoidosis, there is a need for further studies regarding optimal vaccination strategies.

More longitudinal data is needed including large scale epidemiological studies in regard to the prevalence of various infections in sarcoidosis and the role of prophylactic therapy and vaccination in preventing such infections.

Efforts should be made to educate practicing physicians taking care of sarcoidosis patients, as well as patients, to pay special attention to infection prevention and vaccination. A personalized approach to infection prevention and vaccination would serve patients best.

This paper was reviewed and approved by the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) executive committee.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2); 99-103 DOI: 10.36141/svdld.v37i2.8965

The right upper lobe bronchus angle: A tool for differentiating fibrotic and non-fibrotic sarcoidosis

Mary Salvatore[1,3], Danielle Toussie[1], Nadiya Pavlishyn[3], David Yankelevitz[1], Timothy O'Connor[1], Claudia Henschke[1], Maria Padilla[2]

[1]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Department of Radiology, Columbia University Medical Center, New York, NY

Abstract. *Purpose:* To evaluate the Right Upper Lobe Bronchus Angle (RUL-BA) on chest CT in patients with Stage 4 sarcoidosis and compare to others with non-fibrotic sarcoidosis. *Methods:* IRB approval was obtained for review of all chest CT scans performed from January 2015 through December 2017 that contained the word sarcoidosis using the computer program Montage. The most recent CT scans of 633 people were reviewed. The patients' age and sex at the time of their most recent CT scan were recorded. The radiographic diagnosis and the Right Upper Lobe Bronchus Angle (RUL-BA) were determined by a chest radiologist with 20 years of experience. *Results:* The RUL-BA increased with Stage 4 sarcoidosis, measuring on average 104 degrees, compared to the average angle of 88 degrees for those without fibrotic sarcoid. More often men's CT scans exhibited the earlier stages of sarcoidosis, and a higher number of women's scans showed fibrotic sarcoidosis. As would be expected, scans with advanced disease were typically from older patients; however, there was no correlation between age and degree of fibrosis as measured by increasing RUL-BA. *Conclusion:* The RUL-BA assists radiologists in differentiating fibrotic sarcoidosis from non-fibrotic sarcoidosis. Further research will determine if the RUL-BA measurement can help differentiate fibrotic sarcoid from other fibrotic lung diseases and if the angle can be used to follow disease progression. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 99-103)*

Key words: pulmonary fibrosis, chest CT scan, sarcoid

Introduction

Sarcoidosis was first described by Hutchinson in 1869 (1). The exact cause of Sarcoidosis remains unknown, but an unidentified inhaled antigen is suspected because of the cell-mediated response (2) and lung involvement in 90% of patients (1). The prevalence of sarcoidosis in the United States is reported as 50 per 100,000 among Caucasians and 141 per 100,000 among African Americans. The fibrotic form of the disease has a 16% 10-year mortality rate and is associated with significant morbidity caused by concomitant aspergillosis, pulmonary artery hypertension and respiratory exacerbations (2).

Classically the Scadding Staging System (SSS) has been used to group Sarcoidosis into 5 stages based on chest x-ray findings. Stage 0 is normal lung, Stage 1 demonstrates hilar lymphadenopathy, Stage 2 has parenchymal nodules and hilar lymphadenopathy, Stage 3 has parenchymal nodules alone and Stage 4 has fibrotic lung disease (3). The Scadding Staging System can be applied to findings on cross sectional imaging, which is more sensitive and parallels findings on pathology including perilymphatic distribution of parenchymal abnormalities (4).

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Correspondence: Mary Salvatore, M.D MBA
Department of Radiology
Columbia University Medical Center
Tel: 212-305-2094
E-mail: ms5680@cumc.columbia.edu

Stage 4 Sarcoidosis occurs in 20-25% of patients affected with the disease. It is irreversible and may require lung transplant as anti-inflammatory medications are usually ineffective at this stage. Stage 4 Sarcoidosis may cause a diagnostic challenge to differentiate from other types of fibrosis. Posterior displacement of the upper lobe bronchus due to volume loss is a known feature of the fibrotic stage (5). We suggest a method to quantify the amount of posterior bronchial displacement, which could potentially follow disease progression.

Methods

IRB approval was obtained for review of all chest CT scans that contained the word sarcoidosis (using the computer program *Montage*), performed from January 2015 through December 2017. The most recent CT scans of these 633 patients were reviewed by an experienced chest radiologist (MMS with 20 years of experience) and a radiology resident using lung window settings (W 1600, L -600). The patients' age and gender were recorded. Patients with a pattern of fibrosis inconsistent with sarcoidosis were excluded.

Sarcoidosis on CT was graded as follows:

Grade 0: No CT evidence of thoracic disease

Grade 1: Mediastinal and/or hilar lymphadenopathy without pulmonary nodules

Grade 2: Mediastinal and/or hilar lymphadenopathy and perilymphatic pulmonary nodules

Grade 3: Pulmonary nodules in a perilymphatic distribution without lymphadenopathy

Grade 4: Sarcoidosis with pulmonary fibrosis

Grade 4 was considered the fibrotic group, while Grades 0 through 3 represented the non-fibrotic group. The angle between a line traversing the right upper lobe bronchus and a sagittal line connecting the sternum to the vertebral body and tangential to the most medial aspect of bronchus was measured and recorded, as drawn below. The angle is called the Right Upper Lobe Bronchus Angle (RUL-BA) (Figure 1 and Figure 2).

The association between having fibrotic sarcoidosis and the RUL-BA was examined via logistic regression models. The full model compared the likelihood of having Stage 4 Sarcoidosis based on RUL-BA, adjusting for age and gender. A stepwise variable selection procedure was employed to find best model fit, as judged by Akaike Information Criterion (AIC). The best model fit for fibrotic sarcoid was found with RUL-BA, adjusting for age. Furthermore, ROC curves were examined to evaluate balance between sensitivity and specificity

Results

Our initial study population consisted of 640 chest CT scans. 7 of these scans were excluded because the patients' right upper lobe had been resected, 69 were excluded because the radiographic diagnosis was not consistent with patterns of sarcoid

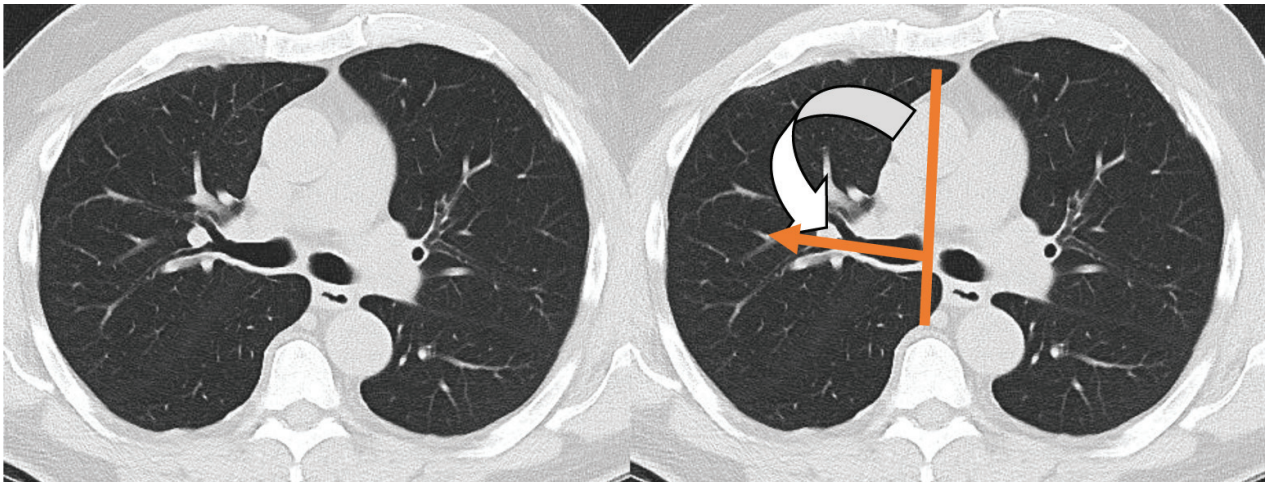

Fig. 1. Normal Right Upper Lobe Bronchial Angle (RUL-BA) measuring 88 degrees

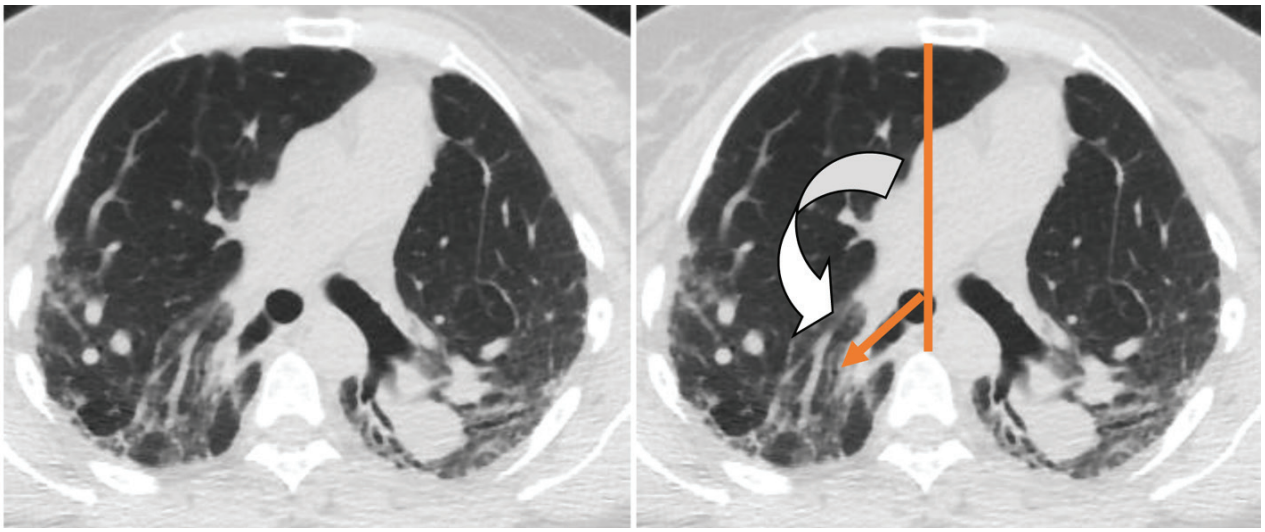

Fig. 2. Right upper lobe posterior predominant fibrosis causing retraction of the right upper lobe bronchus and increase in the Right Upper Lobe Bronchial Angle (RUL-BA) measuring 145 degrees

described in methods section, leaving 564 patients in our study population. The RUL-BA increased with Stage 4 Sarcoidosis, with an average angle of 104 degrees, compared to an average angle of 88 degrees for those without fibrotic sarcoid. As would be expected, scans with the later stage of disease were typically from older patients; however, there was no correlation between age and degree of fibrosis as measured by increasing RUL-BA (Table 1).

The logistic regression analysis resulted in a McFadden Pseudo-R^2 of .39, indicating fair fit. RUL-BA was a significant predictor in the model, with a p value well under $\alpha = .05$ (Table 2).

While holding age constant, for every one-degree increase in RUL-BA above 90 degrees, the odds of having fibrosis were 1.249 times higher. ROC Curve exploration resulted in an 88% in discriminatory ability (Figure 3).

Table 1. Results found on most recent chest CT scan of studied patients

	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
# of patients	148	103	107	45	161
Average age	54 (19-91)	57 (27-90)	55 (30-86)	56 (31-81)	59 (29-94)
% male	58/148 (39%)	52/103 (50%)	60/103 (58%)	24/45 (53%)	70/162 (43%)
Average RULBA	88	87	89	87	104
Range RULBA	73-105	70-104	74-120	67-95	74-145

Table 2. Logistic Regression Analysis Results of Fibrosis based on RULBA and adjusted by age

Predictor	**Coefficient (β)**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
Intercept	-22.633	1.481 x 10^-12	1.182 x 10^-12 - 9.423 10^-9	< 0.0001
RULBA	0.222	1.249	1.954 - 1.314	< 0.0001
Age	0.019	1.02	1.0 - 1.04	0.049

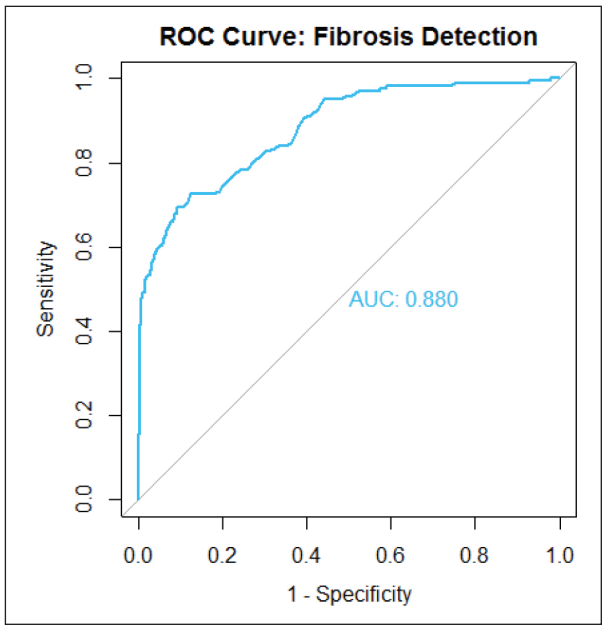

Fig. 3. ROC Curve exploration resulted in a discriminatory ability of 88%

Discussion

The diagnosis of sarcoidosis is made when a patient presents with expected clinical and radiographic findings and pathology showing noncaseating granulomas in a typical peri-lymphatic distribution. Chest x-ray has been used for staging disease with Scadding's Staging System (3). Increasingly, chest CT is used to better define parenchymal abnormalities. In addition, Gallium studies and PET scans are used to determine disease activity and determine if anti-inflammatory medications might be beneficial. The RUL-BA is an ancillary CT tool that can act like an imaging biomarker when it is positive.

Sarcoid is believed to be caused by an unidentified environmental agent as it effects the skin, eyes and lungs. In sarcoid, there is accumulation of granulomas consisting of centrally located macrophages and epitheliod cells surrounded by lymphocytes. The role of the granuloma is to limit inflammation and protect the body. Stage 4 sarcoid occurs when there is an increase in matrix metalloproteinases and a relative decrease in their inhibitors. There is increased fibronectin and CCL18 that increases collagen deposition (6).

Sarcoid is an upper lobe predominant disease along with tuberculosis and hypersensitivity pneumonitis and they all cause the formation of granulomas. The upper lobe to lower lobe lung ventilation ratio is 3:1 whereas the lung lower lobe to upper lobe perfusion ratio is 6:1. Big particles are removed from the trachea by mucociliary clearance, but small particles can get to the alveoli and need to be removed by lymphatics whose function is related to perfusion. The lymphatics work less well in the lung apices, likely the reason why granulomas have an upper lobe predilection (7). Hypersensitivity pneumonitis is caused by an inhaled antigen, so it is not surprising that there is an upper lobe predominant disease. Tuberculosis is inhaled as well, and it also has an upper lobe predilection – but more specifically in the posterior aspects of the upper lobes. Sarcoidosis has the same distribution and in fact, serum samples of patients with sarcoid contain mycobacterial antigen antibodies, supporting the idea that sarcoid is an immune response to environmental pathogen (8).

Lung fibrosis is an end stage disease, but we must differentiate the various types of end stage fibrosis because it will potentially lead to better outcomes as new treatments are developed. Currently, glucocorticosteroids or second-line drugs (methotrexate or azathioprine) are still recommended, monoclonal antibodies have a limited application in patients with sarcoidosis; anti-fibrotics are currently in clinical trials. Preliminary results using mesenchymal cells obtained from umbilical cord blood show promise for treating sarcoidosis (9). Although there are limited options for treatment of end-stage fibrosis, as treatments are developed the importance of a simple and specific diagnostic test will increase. The use of the RUL-BA can help differentiate patients with fibrotic versus non-fibrotic sarcoid which is important because the treatments and prognosis is different.

Our study has limitations. The use of Montage to identify patients with the word sarcoid in their report has potentially caused selection bias, additional research will be needed in patients with a clinical diagnosis of sarcoid, which was staged with chest x-ray to see if the angle can be used as a tool to differentiate fibrotic from nonfibrotic disease on cross sectional imaging.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (1); 104-135 DOI: 10.36141/svdld.v37i1.9142

Sarcoidosis and increased risk of comorbidities and mortality in sweden

Johanna Larsson[1]; Pål Graff[2]; Ing-Liss Bryngelsson[1]; Per Vihlborg[1]*
1 Department of Occupational and Environmental Medicine, Örebro University Hospital, Örebro, Sweden; 2 National Institute of Occupational Health, Department of Chemical and Biological Work Environment, Oslo, Norway

Abstract. *Introduction:* Sarcoidosis is a systemic inflammatory disorder, with an unclear etiology, involving granuloma formation that in most cases affects the lungs and intrathoracic lymph nodes. Sarcoidosis occurs in an acute or chronic form, each with different clinical presentation and prognosis. *Methods:* Case-control study of comorbidity and mortality in people diagnosed with sarcoidosis (ICD10 code D86) from 2007 through 2016 in Sweden. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis. Data was collected from the Swedish National Patient Register and The Cause of Death Register. All men and women aged 20-65 years old who were diagnosed with sarcoidosis (D86, ICD10) during the years of study were included, resulting 7828 cases and 15656 controls. *Results:* Patients with sarcoidosis had increased mortality compared to matched controls (hazard ratio 1.88; 95% CI 1.56 – 2.26) and the Swedish general population (standardized mortality ratios1.75; 95% CI 1.52 – 2.00). The sarcoid cases, compared to controls, also had a significantly greater number of inpatient visits within several different chapters of ICD10 e.g. cardiomyopathy, heart failure, pulmonary embolism and malignant neoplasm. *Conclusion:* Individuals with sarcoidosis are at higher risk of comorbidities and mortality than matched controls as well as the general population of Sweden. These findings are important knowledge for healthcare professionals who meet sarcoid patients, to encourage identification and treatment of comorbidities to reduce the risk of impaired quality of life and, eventually, premature death. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 104-135)*

Key words: Sarcoidosis, Case control, Comorbidity, Mortality

Introduction

Sarcoidosis is a systemic inflammatory disorder involving granuloma formation that, in more than 90% of cases, affects the lungs and intrathoracic lymph nodes. Of all patients, 30-50% show extra pulmonary disease affecting, most commonly, the skin, liver, eyes and peripheral lymph nodes. Sarcoidosis is diagnosed by biopsy of the affected organs. The etiology is unclear, but a genetic susceptibility to yet unidentified environmental factors is suggested (1). Most cases occur sporadically, but some are familial, and first-degree relatives of patients are at a higher risk of developing sarcoidosis than others (2). The annual incidence of sarcoidosis in Sweden is 11.5 per 100 000, among the highest worldwide (3).

Sarcoidosis occurs in an acute or chronic form, each with different clinical presentation and prognosis (1). Most deaths due to sarcoidosis are caused by advanced pulmonary fibrosis or involvement of the central nervous system or heart (4). Studies suggest increased coexistence of several immune-mediated

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Correspondence: Pål Graff
National Institute of Occupational Health,
Department of Chemical and Biological Work Environment,
PO Box 5330 Majorstuen, 0304 Oslo, Norway
E-mail: pal.graff@stami.no

and chronic inflammatory diseases with sarcoidosis (5, 6). Associations with hypertonia, chronic obstructive pulmonary disease (COPD), thyroid diseases, and diabetes mellitus have also been identified (5-10).

Whether the risk of malignancy in sarcoidosis is increased or not has been debated. A meta-analysis including 16 original studies and more than 25,000 patients suggested a moderate, though significant, association between sarcoidosis and malignancy overall (11). Similar results were obtained in a study of hospitalized patients with sarcoidosis in Sweden (12).

Previous studies on mortality in sarcoidosis are largely based on data from death certificates (13-15). Inclusion in these mortality studies requires correct identification of a sarcoidosis case and declaration of sarcoidosis as cause of death on the death certificate. Since sarcoidosis can be a chronic disease affecting several organs there is a risk of misclassification and it may not by declared as the cause of death in patients with a clinically concealed disease. Moreover, patients who had sarcoidosis earlier in life that improved spontaneously would be excluded.

Mortality studies also have contradictory results, with some suggesting that mortality is up to twice as high among those with sarcoidosis compared to the general population while others propose that mortality is not increased in patients with sarcoidosis (16-18). Considering this, this study aimed to contribute with more information on the comorbidities and risk of mortality of sarcoidosis compared to matched controls and the Swedish general population.

Material and Methods

In Sweden, all residents have equal access to publicly funded healthcare and residents have a unique personal identification number that can be used to link data across different nationwide register. The National Board of Health and Welfare (NBHW) holds several registers, including the National Patient Register (NPR). Information on hospitalizations (inpatient register) and non-primary care outpatient visits (outpatient register) can be gathered from the NPR. Another register, The Cause of Death Register, provides the basis for official statistics on both main and contributory causes of death in Sweden. These registers have a high degree of coverage due to reporting obligations. The outpatient register was used to identify cases for the study population. The Cause of Death Register provided information on date and cause of eventual death. Statistics Sweden is another Swedish authority accountable for many registers, including The Multi-Generation Register and The National Register of the Total Population, both used in this study to identify controls.

All data processing conducted to match data from the different registers was performed by the NBHW and Statistics Sweden and de-identified data recorded from 2005 – 2016 was received.

Study population

The study population comprised of men and women aged 20 to 65 years (the typical working age in Sweden) diagnosed with sarcoidosis according to the outpatient register from January 1, 2005 through December 31, 2016. Sarcoidosis was defined according to the ICD10 code D86. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis (Figure 1). The controls selected did not themselves have sarcoidosis, nor were they a first-degree relative of any case. The study population derived from a larger source of material that formed the basis of another study, thus neither the cases nor the controls are diagnosed with Ankylosing spondylitis-M45, Rheumatoid arthritis-M05 and -MO6, Crohn's disease-K50 or Ulcerative colitis-K51. To include as many newly-diagnosed cases and as few revisits as possible, a wash-out was performed over the years 2005-2006 to ensure that only newly-diagnosed cases was used in the statistical calculations.

To estimate comorbidities, information from the inpatient register about the main diagnoses provided on the first visit (date) after the date of the diagnosis of sarcoidosis in respective chapters of ICD10 was collected. Each individual can appear within several different chapters of the ICD10.

Statistical analysis

Demographics are presented using descriptive statistics and is reported as number (n), percentage (%), and mean ± standard deviation (SD). Using Cox regression, sarcoid cases were compared with their controls, and the results are presented as hazard ratios (HR) with 95% confidence intervals (CIs). Study subjects contributed person years from the date they received their sarcoidosis diagnosis to

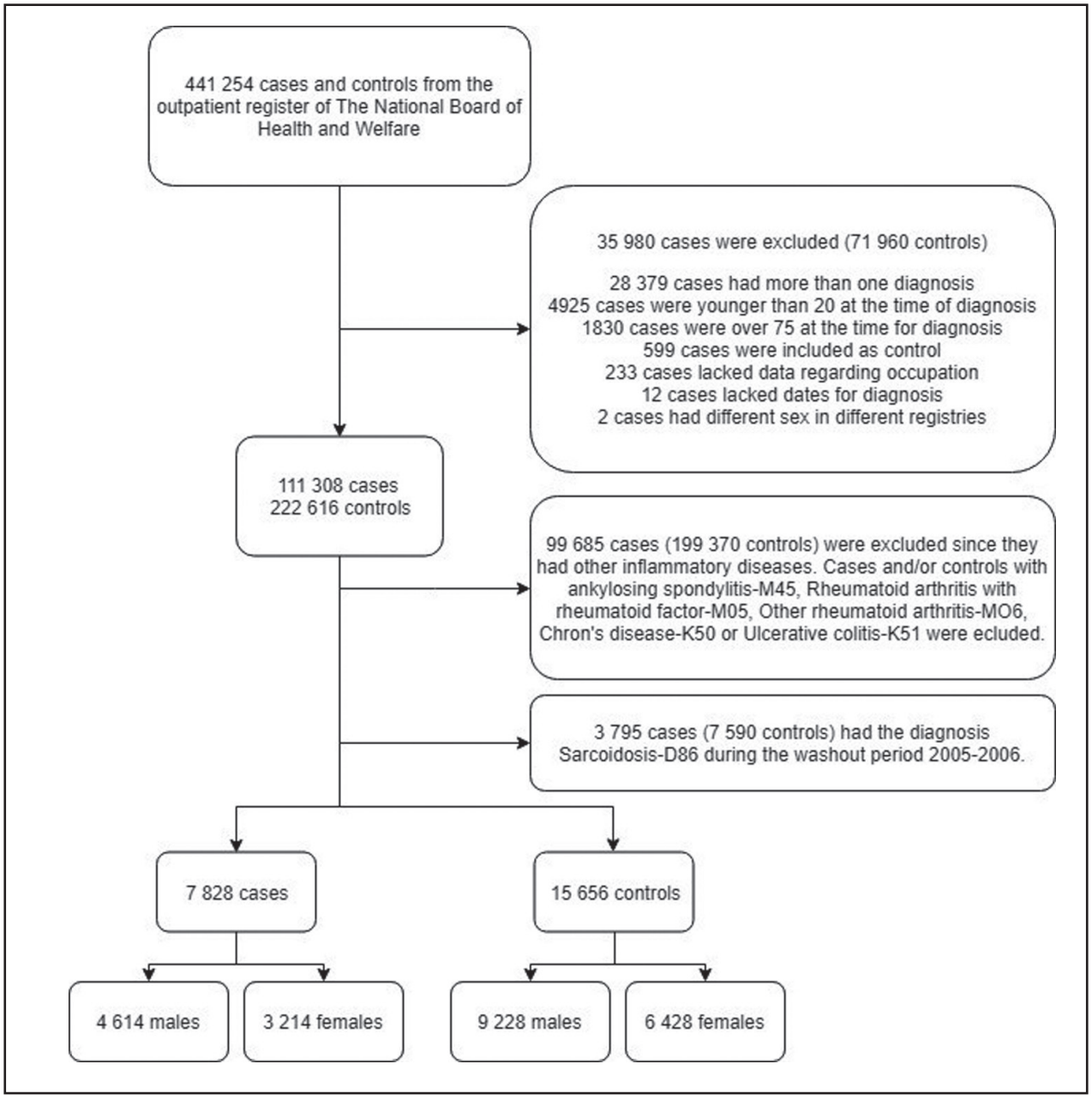

Fig. 1. Flow chart that visualizes inclusion and exclusion of the study population.

the date of event (that is, comorbidity and/or death), emigration or end of the study. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were used to compare sarcoid cases and controls against the general population. With the general population in Sweden used as a reference, data was stratified according to sex, 5-year age groups and 1-year calendar periods when calculating person-years at risk. Assuming a Poisson distribution of the observed numbers, SIRs and SMRs was calculated with 95% CIs. P-values less than 0.05 were considered statistically significant. All analyzes were made using STATA 14.0 (StataCorp LLC, TX; USA).

Ethics

The Swedish Ethical Review Authority (Ref 2017/252) approved the study protocol.

Results

The study population consisted of 23,484 individuals in total, 7828 cases and 15,656 controls. The sex distribution was 58.9% males, 41.1% females. Deaths occurred in a total of 451 individuals, of which 218 (2.8%) were among the cases and 233 (1.5%) were among the controls. Further demographics are presented in Table 1.

Comorbidity

Comparisons of cases and matched controls

The number of inpatient care visits by sarcoid patients, compared to controls, were significantly increased and were associated with diagnoses in most ICD10 chapters, as shown in Table 2. The most apparent increase among sarcoid patients were found in diseases of the blood and immune-mechanism (chapter III), HR 66.48 (95% CI 36.48 – 121.12), which most likely is due to sarcoidosis itself.

Apart from diseases of the blood and immune-mechanism (chapter III), the HRs were highest for: diseases of the eye and adnexa, HR 2.95 (95% CI 1.88 – 4.62); respiratory system, HR 2.76 (95% CI 2.22 – 3.45); and certain infectious and parasitic diseases, HR 2.49 (95% CI 1.84 – 3.38). Further significant increases in associated comorbidities stratified into ICD10 chapters are presented in Table 2. Further information about specific diseases are found in Supplementary Table 1 and 2.

In respiratory system several diagnoses has a higher rate than controls. There is an significant increase in pneumothorax (J93) HR 11.53 (95% CI 3.99 - 33.34), influenza and pneumonia (J09-J18) HR 2.98 (CI 2.41 – 3.68), chronic lower respiratory diseases (J40-J47) HR 2.53 (95% CI 1.66 – 3.85) and other respiratory diseases principally affecting the interstitium (J80-J84) HR 2.98 (95% CI 5.26 – 57.42) (see Supplement Files 2).

Compering cases and controls for diseases of the circulatory system there is an increased HR 1.40 (95% CI 1.21 – 1.63) for the whole chapter.

Table 1. Characteristics of Cases and Controls included in the Study.

	Cases (n = 7 828)	**Controls[a] (n = 15 656)**	**Total (n = 23 484)**
Males No. (%)	4 614 (58.9%)	9 228 (58.9%)	13 842
Females No. (%)	3 214 (41.1%)	6 428 (41.1%)	9 642
Age in males at inclusion, mean (SD), y	45 (10.7)	45 (10.7)	
Age in females at inclusion, mean (SD), y	47 (11.5)	47 (11.5)	
Deaths No. (%)	218 (2.8%)	233 (1.5%)	451 (1.9%)
Death due to sarcoidosis No. (%)	23 (10.6%)	0 (0.0%)	23 (5.1%)
Age at death event in males, mean (SD), y	55 (11.2)	59 (9.3)	
Age at death event in males, mean (SD), y	59 (9.0)	59 (8.6)	

[a] Controls are matched 2:1 on age, sex and county at the time of diagnosis

Subgrouping in diagnosis yield pulmonary embolism (I26) HR 4.36 (95% CI 2.26 – 7.07), cardiomyopathy (I42) HR 5.13 (95% CI 2.37 – 11.08), paroxysmal tachycardia (I47) HR 3.27 (95% CI 2.28 – 4.68) and heart failure (I50) HR 3.27 (95% CI 2.28 – 4.68) and where in high rate and significant increased.

For cancer, there was an increase in malignant neoplasms of ill-defined, secondary and unspecified sites (C76–C80) HR 2.38 (95% CI 1.59 - 3.57) and malignant neoplasms of lymphoid, hematopoietic and related tissue (C81-C96) with HR 2.94 (95% CI 1.85 - 4.68).

A small but significant decrease in association of comorbidities in sarcoid cases, was also seen for mental and behavioral diseases (chapter V). However, when cases and controls were stratified by sex, the results are no longer significant.

Comparisons of cases and matched controls with the general population:

When comorbidities of the sarcoid cases and control groups are independently compared to those of the general population of Sweden, it appears that the sarcoid cases contacted the inpatient healthcare

Table 2: Numbers of Visits to Inpatient Care where Sarcoid Cases and Matched Controls are compared using Cox Regression.

Chapters of ICD 10			**Number of visits cases (n)[a]**	**Number of visits controls (n)[a]**	**HR[b] (95% CI)[c]**
Certain infectious and parasitic diseases	I	Total	93	75	2.49 (1.84 – 3.38)*
		Male	51	39	2.63 (1.73 – 3.99)*
		Female	42	36	2.34 (1.50 – 3.66)*
Neoplasms	II	Total	249	284	1.78 (1.50 – 2.10)*
		Male	133	102	2.64 (2.04 – 3.42)*
		Female	116	182	1.29 (1.02 – 1.62)*
Diseases of the blood and certain immune-mechanisms[d]	III	Total	357	11	66.48 (36.48 – 121.12)*
		Male	215	7	62.96 (29.66 – 133.66)*
Female 142				4	72.61 (26.88 – 196.12)*
Endocrine, nutrional and metabolic disorders	IV	Total	108	107	2.03 (1.55 – 2.65)*
		Male	48	42	2.29 (1.52 – 3.47)*
		Female	60	65	1.86 (1.31 – 2.64)*
Mental and behavioural diseases	V	Total	91	236	0.77 (0.60 – 0.98)*
		Male	63	162	0.78 (0.58 – 1.04)
		Female	28	74	0.76 (0.49 – 1.17)
Diseases of the nervous system	VI	Total	108	94	2.31 (1.75 – 3.04)*
		Male	66	52	2.55 (1.77 – 3.67)*
		Female	42	42	2.01 (1.31 – 3.08)*
Diseases of the eye and adnexa	VII	Total	47	32	2.95 (1.88 – 4.62)*
		Male	25	18	2.78 (1.52 – 5.10)*
		Female	22	14	3.15 (1.61 – 6.16)*
Diseases of the ear and mastoid process	VIII	Total	22	44	1.00 (0.60 – 1.67)
		Male	11	24	0.92 (0.45 – 1.87)
		Female	11	20	1.10 (0.53 – 2.30)
Diseases of the circulatory system	IX	Total	283	407	1.40 (1.21 – 1.63)*
		Male	193	287	1.36 (1.13 – 1.63)*
		Female	90	120	1.51 (1.15 – 1.98)*
Diseases of the respiratory system	X	Total	186	136	2.76 (2.22 – 3.45)*
		Male	110	77	2.89 (2.16 – 3.86)*
		Female	76	59	2.61 (1.86 – 3.66)*
Diseases of the digestive system	XI	Total	221	352	1.26 (1.07 – 1.49)*
		Male	121	208	1.17 (0.93 – 1.46)*
		Female	100	144	1.40 (1.08 – 1.80)*
Diseases of the skin and subcutaneous tissue	XII	Total	27	23	2.35 (1.35 – 4.10)*
		Male	15	14	2.14 (1.04 – 4.44)*
		Female	12	9	2.67 (1.13 – 6.34)*

Chapters of ICD 10			Number of visits cases (n)[a]	Number of visits controls (n)[a]	HR[b] (95% CI)[c]
Diseases of the musculoskeletal system and connective tissue	XIII	Total	183	327	1.12 (0.94 – 1.34)
		Male	101	178	1.14 (0.89 – 1.45)
		Female	82	149	1.10 (0.84 – 1.44)
Diseases of the genitourinary system	XIV	Total	297	302	2.00 (1.70 – 2.34)*
		Male	143	151	1.91 (1.52 – 2.40)*
		Female	154	151	2.08 (1.66 – 2.61)*
Pregnancy, childbirth and the puerperium	XV	Total	280	584	0.96 (0.83 – 1.10)
		Female	280	584	0.95 (082 – 1.10)
Congenital malformations and chromosomal abnormalities	XVII	Total	2	10	0.40 (0.09 – 1.86)
		Male	1	6	0.33 (0.04 – 2.77)
		Female	1	4	0.50 (0.06 – 4.47)
Symptoms and abnormal findings[e]	XVIII	Total	368	375	1.99 (1.73 – 2.30)*
		Male	209	215	1.97 (1.63 – 2.39)*
		Female	159	160	2.02 (1.63 – 2.52)*
Injury, poisoning & certain other consequences of external causes	XIX	Total	200	362	1.11 (0.93 – 1.31)
		Male	133	232	1.15 (0.93 – 1.42)
		Female	67	133	1.03 (0.77 – 1.38)
Factors influencing health status[f]	XXI	Total	93	96	1.95 (1.46 – 2.59)*
		Male	41	45	1.82 (1.20 – 2.79)*
		Female	52	51	2.05 (1.39 – 3.02)*

[a] Each individual can appear several times in different chapters, [b] Hazard ratio, [c] 95% confidence interval, [d] Diseases of the blood and blood-forming organs and certain disorders involving the immune-mechanism, [e] Symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified, [f] Factors influencing health status and contact with health services

clinic significantly more frequently than the general population (Figure 2). The controls, however, contacted the inpatient clinic less frequently than the general population.

Mortality

Comparison between cases and matched controls

Death occurred for 218 cases (2.8%) and for 233 (1.5%) controls. Mortality HR among sarcoid cases were 5.5 (95% CI 4.8 – 6.3) per 1000 person-years, and 2.9 (95% CI 2.6 - 3.3) per 1000 person-years in matched controls. The overall HR for mortality was 1.88 (95% CI 1.56 – 2.26) as seen in Table 3. Mortality caused by neoplasms (chapter II) was significantly increased for sarcoid cases in both males and females. Increased mortality in males, but not in females, was seen for diseases of the circulatory system (chapter IX), respiratory system (chapter X) and external causes of mortality (chapter XX). Increased mortality HR was also seen for diseases of the blood and immune-mechanisms (chapter III) compared to controls, but this increase is probably due to the sarcoidosis-diagnosis itself.

External causes of mortality (chapter XX) includes accidents and intentional death. Of the sarcoid cases, 17 deaths were due to accidents and 10 were intentional. Of the controls, 12 died due to accidents, and 12 deaths were intentional.

Table 3 presents only the ICD10 chapters where at least five deaths among cases or controls

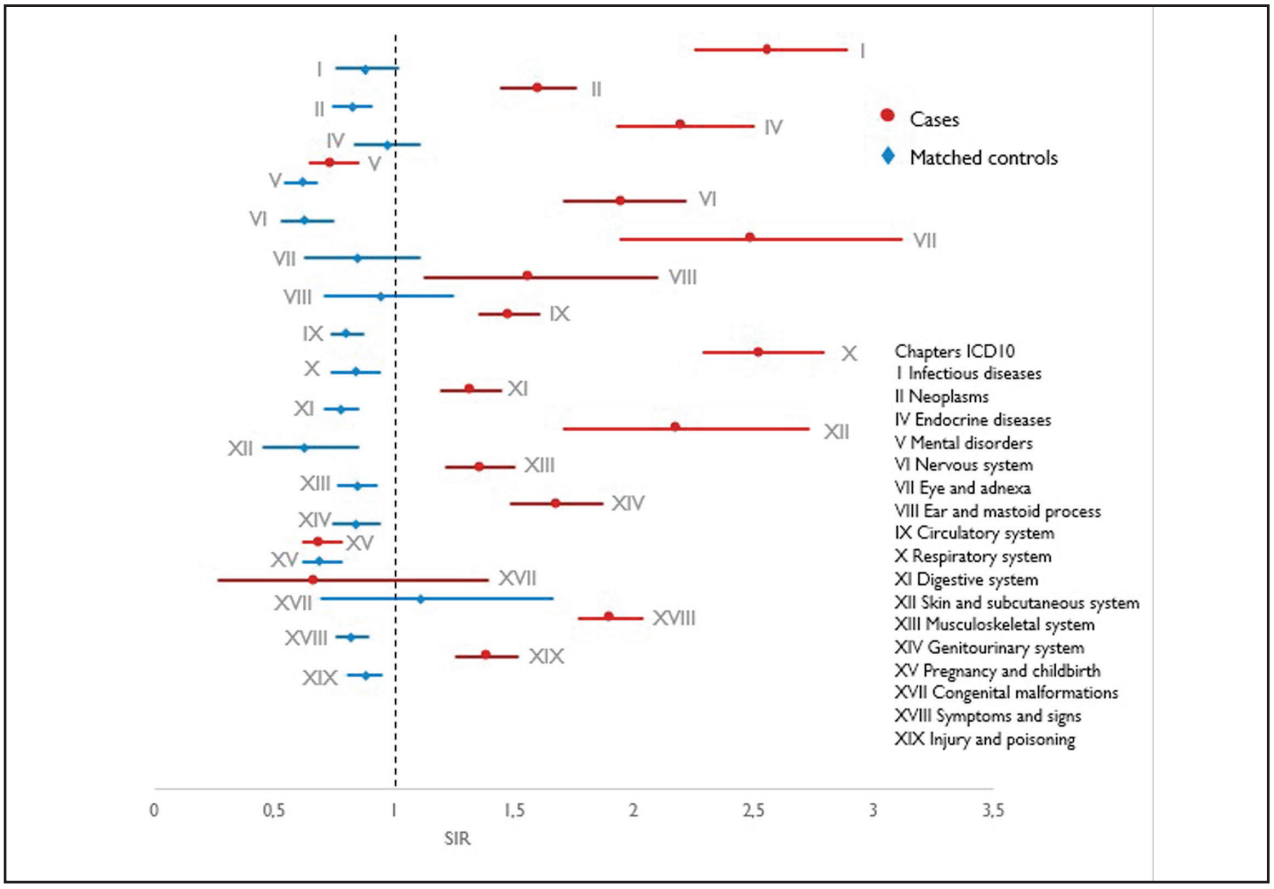

Fig. 2. Comparison of Comorbidities between Cases/Controls and the General Population. Every unique personal identification number was counted once a year, per chapter and county.

are declared. Seven deaths among the cases and six deaths among the controls were therefore not included in the table but are included in the analysis of total mortality.

Comparison of cases and matched controls with the general population:

Total overall mortality for sarcoid cases was greater than the general population, SMR 1.75 (95% CI 1.52-2.00). There was no significant difference in mortality between controls and the general population. Significantly more deaths were observed for sarcoid cases than for the general population due to neoplasms (chapters II), diseases of the respiratory system (chapter X) and external causes of mortality (chapter XX) as illustrated in Figure 3. These findings differ from the results of the comparison between sarcoid cases and matched controls, which demonstrated a small increase in mortality caused by cardiovascular diseases, HR 1.64 (95% CI 1.08 – 2.48).

Discussion

In this longitudinal case-control study, the aim was to examine comorbidities and mortality in sarcoid patients in Sweden during the years 2007 – 2016. Increases in overall comorbidity and overall mortality in sarcoid patients compared to matched controls as well as the general population was observed during the observation period.

Sarcoid patients showed increased overall comorbidity compared to controls. Sarcoidosis is a systemic disease that manifests in several organs. Each organ manifestation has its own code in the ICD10, and these codes are found across several different chapters. Examples of codes include: G35-Cranial

Table 3. Deaths in Sarcoid Cases and Matched Controls Compared using Cox Regression.

Chapters of ICD 10[a]			Deaths cases (n)	Deaths controls (n)	HR[b] (95% CI)[c]
Total		Total	218	233	1.88 (1.56 – 2.26)*
		Male	131	149	1.76 (1.39 – 2.23)*
		Female	87	84	2.08 (1.54 – 2.81)*
Neoplasms	II	Total	90	110	1.64 (1.24 – 2.17)*
		Male	45	61	1.48 (1.00 – 2.17)
		Female	45	49	1.85 (1.23 – 2.77)*
Diseases of the blood and certain immune-mechanisms[d]	III	Total	24	1	48.15 (6.51 – 355.92)*
		Male	13	1	26.00 (3.40 – 198.75)*
		Female	11	0	-
Endocrine, nutrional and metabolic diseases	IV	Total	7	8	1.75 (0.64 – 4.84)
		Male	3	4	1.50 (0.34 – 6.71)
		Female	4	4	2.02 (0.50 – 8.06)
Diseases of the nervous system	VI	Total	1	9	0.22 (0.03 – 1.76)
		Male	0	7	-
		Female	1	2	1.01 (0.09 – 11.09)
Diseases of the circulatory system	IX	Total	40	49	1.64 (1.08 – 2.48)*
		Male	34	37	1.84 (1.15 – 2.93)*
		Female	6	12	1.00 (0.38 – 2.67)
Diseases of the respiratory system	X	Total	12	7	3.44 (1.36 – 8.74)*
		Male	7	4	3.50 (1.03 – 11.97)*
		Female	5	3	3.37 (0.81 – 14.12)
Diseases of the digestive system	XI	Total	6	11	1.09 (0.40 – 2.96)
		Male	2	5	0.80 (0.16 – 4.13)
		Female	4	6	1.34 (0.38 – 4.75)
Symptoms and abnormal findings[e]	XVIII	Total	4	8	1.00 (0.30 – 3.33)
		Male	1	7	0.29 (0.04 – 2.32)
		Female	3	1	6.00 (0.62 – 57.67)
External causes of morbidity and mortality	XX	Total	27	24	2.26 (1.30 – 3.91)*
		Male	22	19	2.32 (1.25 – 4.28)*
		Female	5	5	2.02 (0.58 – 6.98)

[a] Only chapters where at least 5 deaths are seen in either cases or the controls are reported, [b] Hazard ratio, [c] 95% confidence interval, [d] Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, [e] Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

nerve disorders-, H22-Disorders of iris and ciliary body- and I41-Myocarditis in diseases classified elsewhere. In this study, observations of comorbidities are presented at the ICD10 chapter level instead of analyzing individual diagnoses. Therefore, it is not possible to specify which diagnoses are causing the increase.

As mentioned previously, a large meta-analysis suggested that the risk of malignancies increases slightly with sarcoidosis (11). In this study, malignancy was one of the most common reasons patients needed inpatient care, HR 1.78 (95% CI 1.50 – 2.10), which support this observation. Only cardiovascular diseases led to as many, and slightly more, inpatient

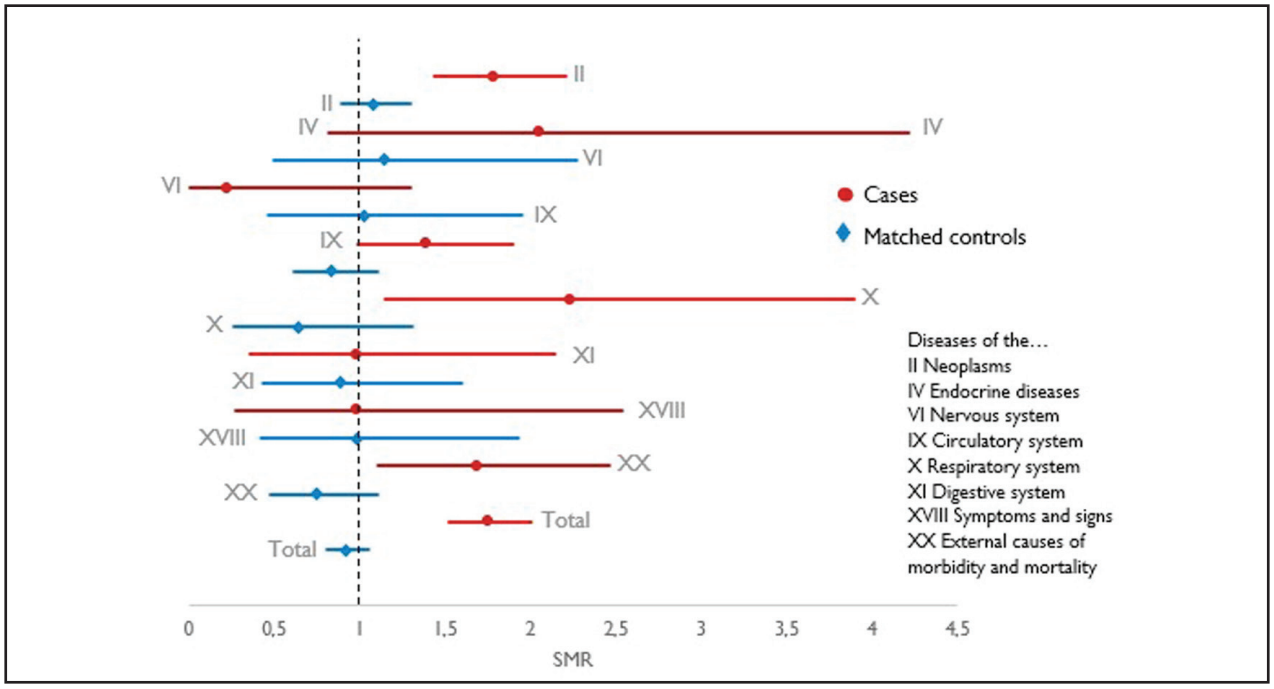

Fig. 3. Comparison of Mortality between Cases/Controls and the General Population. Every unique personal identification number was counted only once a year, per chapter and county. Only chapters with 5 or more deaths among cases or controls are included.

visits, but for these comorbidities, the difference between cases and controls was not as large, HR 1.40 (95% CI 1.21 – 1.63).

This study reveals increased mortality in sarcoid cases compared to controls, with death occurring in 2.8% of sarcoid cases and 1.5% of controls, HR 1.88 (95% CI 1.56–2.26). In previous studies, mortality rates have ranged between 9.4-14 per 1000 person-years (13, 14, 16). A recently-published Swedish study on mortality in sarcoid patients aged 18-85 years showed a mortality rate of 11 per 1000 person-years, while controls had a mortality rate of 6.7 per 1000 person-years (19). This study showed mortality rates of 5.5 (95% CI 4.8 – 6.3) per 1000 person-years among sarcoid cases and 2.9 (95% CI 2.6- 3.3) per 1000 person-years in matched controls. The lower mortality rate observed in this study might be due to the younger study population (aged 20-65 years), or to the somewhat healthier populations since neither the cases nor the controls suffered from ankylosing spondylitis, rheumatoid arthritis, Crohn's disease or ulcerative colitis.

The ICD10 chapter associated with the highest increased risk of death was diseases of the blood and immune-mechanism (c*hapter III), where the code for sarcoidosis diagnosis is found*. Previously, sarcoidosis was reported to account for 24.7-58.8% of deaths occurring among sarcoid patients (14, 17). In this study, sarcoidosis was considered the cause of death in 10.6% of deaths among sarcoid patients. In Scandinavia, one third of sarcoid patients is affected by the acute form, Lofgren's syndrome, rather than the chronic form. Lofgren's syndrome is said to have a better prognosis. The cause of death among cases evaluated in this study may be affected by low reporting of sarcoidosis as the cause of death among patients, since patients may have suffered from Lofgren's syndrome earlier in life and were considered recovered at the time of death. Another impact to mortality, as evaluated herein, is that the downstream consequences of the patients' sarcoidosis were coded as the cause of death rather than the sarcoidosis diagnosis itself.

The ICD10 chapters associated with the highest number of deaths among sarcoid cases was neoplasms (90 deaths, 41.3%), cardiovascular diseases (40 deaths, 18.3%), external causes of mortality (27 deaths, 12.4%) and respiratory diseases (12 deaths,

5.5%). A study investing sarcoidosis-related morality in France, cardiovascular and respiratory diseases accounted for 16.8% and 7.5% of underlying causes of death while sarcoidosis was listed as a non-underlying cause of death, which is similar to the findings of this study (13). However, neoplasms accounted for 24.7% of the underlying cause of deaths which is clearly lower than the findings in this study (13).

Suicide is a cause of death included in external causes of mortality (chapter XX) and, in males, this chapter was associated with a significant increase in death compared to controls, HR 2.32 (95% CI 1.25 – 4.98). It has previously been reported that the prevalence of depression in patients with sarcoidosis may be up to 60% when a standardized protocol is used to identify depression (20). However, this study show no increased number of visits to inpatient care for mental and behavioural diseases (chapter V). One explanation for this finding might be that depression was under-diagnosed among the study cases. Another, possibly more likely explanation may be that mild to moderate depression is usually treated in primary care, but this study used data from the inpatient register only.

One limitation of this study was that it is not possible stratify sarcoid cases by level of severity of sarcoidosis or type of sarcoidosis (acute or chronic form). Another limitation, as this is a register study, there was no information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area and therefore one could assume the distribution of smokers and non-smokers to be similar in both groups. Furthermore, there was no information about medications, which also could be a confounder, as medications used to treat sarcoidosis can cause varying side effects. For instance Glucocorticoids, the first-line therapy, have numerous side effects that affect several different organ systems (21).

The strengths of this study is study is the large study population comprising 7828 cases and 15,656 matched controls, and cases and controls were also both compared to the general population. Moreover, Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers, and therefore it was possible, with few exceptions, to include anyone who was diagnosed with sarcoidosis in the years 2007-2016, and not just a selection.

In conclusion, individuals with sarcoidosis are at higher risk of comorbidities and mortality compared to matched controls as well as the general population. Thus healthcare professionals who meet sarcoid patients, should strive to identify and treat comorbidities to reduce the risk of impaired quality of life and, eventually, premature death among individuals with sarcoidosis.

Conflict of Interest: None

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Supplement Table 1: Visits to Inpatient Care for the all diseases found among Cases and Controls (ratio for cases/control is 1:2). Only one registration for each disease were counted, i.e. multiple visits due to the same disease are only counted as one.

Diagnosis	ICD 10	Cases	Control*
		number	
Other salmonella infections	A02	0	1
Other bacterial intestinal infections	A04	22	21
Other bacterial foodborne intoxications, not elsewhere classified	A05	1	0
Other protozoal intestinal diseases	A07	2	1
Viral and other specified intestinal infections	A08	16	2
Other gastroenteritis and colitis of infectious and unspecified origin	A09	39	22
Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	3	3
Respiratory tuberculosis, not confirmed bacteriologically or histologically	A16	3	1
Tuberculosis of nervous system	A17	1	0
Tuberculosis of other organs	A18	3	0
Miliary tuberculosis	A19	1	0
Tularaemia	A21	0	1
Erysipeloid	A26	0	1
Infection due to other mycobacteria	A31	3	0
Streptococcal sepsis	A40	8	4
Other sepsis	A41	53	37
Erysipelas	A46	45	40
Other bacterial diseases, not elsewhere classified	A48	3	1
Bacterial infection of unspecified site	A49	20	13
Anogenital herpesviral [herpes simplex] infection	A60	1	1

Diagnosis	ICD 10	Cases	Control*
Other predominantly sexually transmitted diseases, not elsewhere classified	A63	1	0
Other spirochaetal infections	A69	1	0
Tick-borne viral encephalitis	A84	1	1
Viral meningitis	A87	6	3
Dengue fever [classical dengue]	A90	0	1
Other viral haemorrhagic fevers, not elsewhere classified	A98	3	0
Herpesviral [herpes simplex] infections	B00	3	1
Varicella [chickenpox]	B01	1	0
Zoster [herpes zoster]	B02	6	4
Chronic viral hepatitis	B18	4	2
Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	B20	2	0
Cytomegaloviral disease	B25	5	1
Infectious mononucleosis	B27	0	2
Viral infection of unspecified site	B34	26	8
Candidiasis	B37	4	4
Histoplasmosis	B39	1	0
Aspergillosis	B44	5	0
Plasmodium falciparum malaria	B50	1	1
Pneumocystosis	B59	4	1
Sequelae of tuberculosis	B90	1	0
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95	0	2
Other specified bacterial agents as the cause of diseases classified to other chapters	B96	2	0
Other and unspecified infectious diseases	B99	11	12
Malignant neoplasm of base of tongue	C01	2	3
Malignant neoplasm of other and unspecified parts of tongue	C02	3	0
Malignant neoplasm of gum	C03	1	1
Malignant neoplasm of palate	C05	0	1
Malignant neoplasm of other and unspecified parts of mouth	C06	1	0
Malignant neoplasm of parotid gland	C07	0	2
Malignant neoplasm of other and unspecified major salivary glands	C08	1	0
Malignant neoplasm of tonsil	C09	4	2
Malignant neoplasm of oesophagus	C15	0	1
Malignant neoplasm of stomach	C16	0	4
Malignant neoplasm of small intestine	C17	1	0
Malignant neoplasm of colon	C18	22	15
Malignant neoplasm of rectum	C20	7	13
Malignant neoplasm of anus and anal canal	C21	1	0
Malignant neoplasm of liver and intrahepatic bile ducts	C22	2	6
Malignant neoplasm of other and unspecified parts of biliary tract	C24	0	4
Malignant neoplasm of pancreas	C25	4	5
Malignant neoplasm of nasal cavity and middle ear	C30	1	0
Malignant neoplasm of accessory sinuses	C31	1	0

Diagnosis	ICD 10	Cases	Control*
Malignant neoplasm of larynx	C32	1	0
Malignant neoplasm of bronchus and lung	C34	13	26
Malignant neoplasm of thymus	C37	1	1
Malignant neoplasm of bone and articular cartilage of limbs	C40	1	1
Malignant melanoma of skin	C43	8	9
Other malignant neoplasms of skin	C44	6	4
Mesothelioma	C45	2	0
Malignant neoplasm of retroperitoneum and peritoneum	C48	2	4
Malignant neoplasm of other connective and soft tissue	C49	3	4
Malignant neoplasm of breast	C50	22	66
Malignant neoplasm of cervix uteri	C53	4	4
Malignant neoplasm of corpus uteri	C54	6	13
Malignant neoplasm of ovary	C56	8	8
Malignant neoplasm of other and unspecified female genital organs	C57	1	1
Malignant neoplasm of penis	C60	2	0
Malignant neoplasm of prostate	C61	25	35
Malignant neoplasm of testis	C62	1	1
Malignant neoplasm of kidney, except renal pelvis	C64	8	9
Malignant neoplasm of renal pelvis	C65	0	3
Malignant neoplasm of ureter	C66	0	1
Malignant neoplasm of bladder	C67	7	20
Malignant neoplasm of eye and adnexa	C69	1	0
Malignant neoplasm of brain	C71	5	8
Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	C72	1	0
Malignant neoplasm of thyroid gland	C73	5	2
Malignant neoplasm of adrenal gland	C74	1	0
Malignant neoplasm of other and ill-defined sites	C76	1	0
Secondary and unspecified malignant neoplasm of lymph nodes	C77	8	11
Secondary malignant neoplasm of respiratory and digestive organs	C78	23	20
Secondary malignant neoplasm of other and unspecified sites	C79	23	16
Malignant neoplasm, without specification of site	C80	4	0
Hodgkin lymphoma	C81	7	0
Follicular lymphoma	C82	0	1
Non-follicular lymphoma	C83	10	8
Mature T/NK-cell lymphomas	C84	4	1
Other and unspecified types of non-Hodgkin lymphoma	C85	14	6
Other specified types of T/NK-cell lymphoma	C86	3	0
Malignant immunoproliferative diseases	C88	2	2
Multiple myeloma and malignant plasma cell neoplasms	C90	4	11
Lymphoid leukaemia	C91	3	2
Myeloid leukaemia	C92	5	1
Monocytic leukaemia	C93	1	0

Diagnosis	ICD 10	Cases	Control*
Leukaemia of unspecified cell type	C95	0	1
Carcinoma in situ of other and unspecified digestive organs	D01	1	0
Carcinoma in situ of breast	D05	4	7
Carcinoma in situ of cervix uteri	D06	4	1
Carcinoma in situ of other and unspecified genital organs	D07	2	0
Benign neoplasm of mouth and pharynx	D10	0	1
Benign neoplasm of major salivary glands	D11	4	4
Benign neoplasm of colon, rectum, anus and anal canal	D12	4	7
Benign neoplasm of other and ill-defined parts of digestive system	D13	2	1
Benign neoplasm of middle ear and respiratory system	D14	9	1
Benign neoplasm of bone and articular cartilage	D16	1	2
Benign lipomatous neoplasm	D17	2	4
Haemangioma and lymphangioma, any site	D18	1	1
Benign neoplasm of soft tissue of retroperitoneum and peritoneum	D20	2	1
Other benign neoplasms of connective and other soft tissue	D21	2	3
Benign neoplasm of breast	D24	1	1
Leiomyoma of uterus	D25	18	46
Benign neoplasm of ovary	D27	5	11
Benign neoplasm of male genital organs	D29	1	0
Benign neoplasm of urinary organs	D30	1	0
Benign neoplasm of eye and adnexa	D31	3	0
Benign neoplasm of meninges	D32	8	6
Benign neoplasm of brain and other parts of central nervous system	D33	2	0
Benign neoplasm of thyroid gland	D34	1	3
Benign neoplasm of other and unspecified endocrine glands	D35	10	8
Benign neoplasm of other and unspecified sites	D36	3	0
Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs	D37	20	15
Neoplasm of uncertain or unknown behaviour of middle ear and respiratory and intrathoracic organs	D38	79	5
Neoplasm of uncertain or unknown behaviour of female genital organs	D39	5	6
Neoplasm of uncertain or unknown behaviour of male genital organs	D40	3	0
Neoplasm of uncertain or unknown behaviour of urinary organs	D41	7	11
Neoplasm of uncertain or unknown behaviour of brain and central nervous system	D43	12	11
Neoplasm of uncertain or unknown behaviour of endocrine glands	D44	6	7
Myelodysplastic syndromes	D46	1	0
Other neoplasms of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue	D47	1	2
Neoplasm of uncertain or unknown behaviour of other and unspecified sites	D48	7	10
Iron deficiency anaemia	D50	17	8
Vitamin B12 deficiency anaemia	D51	0	1
Other nutritional anaemias	D53	0	1
Acquired haemolytic anaemia	D59	3	1

Diagnosis	ICD 10	Cases	Control*
Other aplastic anaemias	D61	1	1
Acute posthaemorrhagic anaemia	D62	1	2
Other anaemias	D64	14	20
Other coagulation defects	D68	3	1
Purpura and other haemorrhagic conditions	D69	4	3
Agranulocytosis	D70	14	3
Other disorders of white blood cells	D72	0	1
Diseases of spleen	D73	2	1
Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue	D76	2	0
Immunodeficiency associated with other major defects	D82	1	1
Common variable immunodeficiency	D83	0	1
Other immunodeficiencies	D84	1	0
Sarcoidosis	D86	526	0
Other hypothyroidism	E03	0	3
Other nontoxic goitre	E04	12	15
Thyrotoxicosis [hyperthyroidism]	E05	6	9
Thyroiditis	E06	1	1
Other disorders of thyroid	E07	0	1
Type 1 diabetes mellitus	E10	19	24
Type 2 diabetes mellitus	E11	51	36
Other specified diabetes mellitus	E13	2	0
Unspecified diabetes mellitus	E14	2	1
Nondiabetic hypoglycaemic coma	E15	0	1
Other disorders of pancreatic internal secretion	E16	2	3
Hyperparathyroidism and other disorders of parathyroid gland	E21	13	6
Hyperfunction of pituitary gland	E22	0	2
Hypofunction and other disorders of pituitary gland	E23	5	0
Other disorders of adrenal gland	E27	6	1
Other endocrine disorders	E34	1	0
Unspecified severe protein-energy malnutrition	E43	1	0
Unspecified protein-energy malnutrition	E46	3	1
Thiamine deficiency	E51	0	3
Localized adiposity	E65	7	4
Obesity	E66	84	79
Sequelae of hyperalimentation	E68	1	0
Lactose intolerance	E73	1	0
Disorders of sphingolipid metabolism and other lipid storage disorders	E75	0	1
Disorders of lipoprotein metabolism and other lipidaemias	E78	1	3
Disorders of mineral metabolism	E83	18	1
Volume depletion	E86	6	3
Other disorders of fluid, electrolyte and acid-base balance	E87	20	18
Postprocedural endocrine and metabolic disorders, not elsewhere classified	E89	0	2

Diagnosis	ICD 10	Cases	Control*
Dementia in other diseases classified elsewhere	F02	1	0
Unspecified dementia	F03	0	2
Delirium, not induced by alcohol and other psychoactive substances	F05	3	4
Other mental disorders due to brain damage and dysfunction and to physical disease	F06	3	2
Personality and behavioural disorders due to brain disease, damage and dysfunction	F07	0	2
Unspecified organic or symptomatic mental disorder	F09	1	1
Mental and behavioural disorders due to use of alcohol	F10	58	107
Mental and behavioural disorders due to use of opioids	F11	14	20
Mental and behavioural disorders due to use of cannabinoids	F12	1	2
Mental and behavioural disorders due to use of sedatives or hypnotics	F13	9	7
Mental and behavioural disorders due to use of cocaine	F14	1	1
Mental and behavioural disorders due to use of other stimulants, including caffeine	F15	6	4
Mental and behavioural disorders due to use of volatile solvents	F18	0	1
Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances	F19	22	32
Schizophrenia	F20	5	24
Persistent delusional disorders	F22	3	10
Acute and transient psychotic disorders	F23	4	8
Schizoaffective disorders	F25	3	7
Unspecified nonorganic psychosis	F29	3	12
Manic episode	F30	1	3
Bipolar affective disorder	F31	22	31
Depressive episode	F32	40	52
Recurrent depressive disorder	F33	18	27
Persistent mood [affective] disorders	F34	1	0
Unspecified mood [affective] disorder	F39	1	0
Other anxiety disorders	F41	43	40
Obsessive-compulsive disorder	F42	4	5
Reaction to severe stress, and adjustment disorders	F43	26	43
Dissociative [conversion] disorders	F44	4	3
Somatoform disorders	F45	5	0
Other neurotic disorders	F48	1	0
Eating disorders	F50	2	1
Nonorganic sleep disorders	F51	4	2
Specific personality disorders	F60	12	9
Mixed and other personality disorders	F61	0	1
Habit and impulse disorders	F63	1	0
Mild mental retardation	F70	1	3
Moderate mental retardation	F71	1	0
Unspecified mental retardation	F79	0	1
Pervasive developmental disorders	F84	3	4
Hyperkinetic disorders	F90	7	4

Diagnosis	ICD 10	Cases	Control*
Conduct disorders	F91	1	0
Mental disorder, not otherwise specified	F99	3	0
Bacterial meningitis, not elsewhere classified	G00	0	1
Meningitis due to other and unspecified causes	G03	2	2
Encephalitis, myelitis and encephalomyelitis	G04	2	1
Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere	G05	1	0
Intracranial and intraspinal abscess and granuloma	G06	4	0
Hereditary ataxia	G11	1	0
Spinal muscular atrophy and related syndromes	G12	1	4
Parkinson disease	G20	2	3
Dystonia	G24	1	0
Other extrapyramidal and movement disorders	G25	5	2
Alzheimer disease	G30	0	2
Other degenerative diseases of nervous system, not elsewhere classified	G31	1	0
Multiple sclerosis	G35	7	11
Other demyelinating diseases of central nervous system	G37	3	1
Epilepsy	G40	27	34
Status epilepticus	G41	3	0
Migraine	G43	22	14
Other headache syndromes	G44	17	10
Transient cerebral ischaemic attacks and related syndromes	G45	44	40
Sleep disorders	G47	53	22
Disorders of trigeminal nerve	G50	5	2
Facial nerve disorders	G51	10	6
Nerve root and plexus disorders	G54	2	1
Mononeuropathies of upper limb	G56	3	3
Mononeuropathies of lower limb	G57	1	1
Hereditary and idiopathic neuropathy	G60	1	0
Inflammatory polyneuropathy	G61	5	6
Other polyneuropathies	G62	7	2
Polyneuropathy in diseases classified elsewhere	G63	0	1
Other disorders of peripheral nervous system	G64	1	0
Myasthenia gravis and other myoneural disorders	G70	0	1
Primary disorders of muscles	G71	2	1
Other myopathies	G72	1	2
Cerebral palsy	G80	0	1
Hemiplegia	G81	2	3
Paraplegia and tetraplegia	G82	5	1
Other paralytic syndromes	G83	2	3
Disorders of autonomic nervous system	G90	0	1
Hydrocephalus	G91	9	5
Other disorders of brain	G93	5	4

Diagnosis	ICD 10	Cases	Control*
Other diseases of spinal cord	G95	2	2
Other disorders of central nervous system	G96	2	1
Postprocedural disorders of nervous system, not elsewhere classified	G97	1	1
Other disorders of eyelid	H02	2	1
Disorders of lacrimal system	H04	6	1
Disorders of orbit	H05	2	2
Keratitis	H16	2	3
Other disorders of cornea	H18	1	3
Iridocyclitis	H20	1	0
Other cataract	H26	1	1
Chorioretinal inflammation	H30	2	0
Retinal detachments and breaks	H33	18	19
Retinal vascular occlusions	H34	1	3
Other retinal disorders	H35	15	4
Glaucoma	H40	9	0
Disorders of vitreous body	H43	5	6
Disorders of globe	H44	1	1
Optic neuritis	H46	2	0
Other disorders of optic [2nd] nerve and visual pathways	H47	2	0
Paralytic strabismus	H49	4	1
Other strabismus	H50	1	2
Other disorders of binocular movement	H51	0	1
Visual disturbances	H53	5	7
Visual impairment including blindness (binocular or monocular)	H54	1	0
Other disorders of eye and adnexa	H57	1	1
Otitis externa	H60	0	1
Other disorders of external ear	H61	2	0
Nonsuppurative otitis media	H65	0	1
Suppurative and unspecified otitis media	H66	4	3
Cholesteatoma of middle ear	H71	1	2
Perforation of tympanic membrane	H72	1	1
Other disorders of middle ear and mastoid	H74	1	0
Otosclerosis	H80	3	6
Disorders of vestibular function	H81	26	36
Conductive and sensorineural hearing loss	H90	2	2
Other hearing loss	H91	3	2
Rheumatic mitral valve diseases	I05	0	1
Essential (primary) hypertension	I10	18	28
Hypertensive heart disease	I11	2	1
Hypertensive renal disease	I12	1	0
Secondary hypertension	I15	5	0
Angina pectoris	I20	45	77

Diagnosis	ICD 10	Cases	Control*
Acute myocardial infarction	I21	70	141
Subsequent myocardial infarction	I22	0	2
Certain current complications following acute myocardial infarction	I23	0	2
Other acute ischaemic heart diseases	I24	0	1
Chronic ischaemic heart disease	I25	18	28
Pulmonary embolism	I26	52	24
Other pulmonary heart diseases	I27	5	1
Acute pericarditis	I30	10	6
Other diseases of pericardium	I31	6	4
Pericarditis in diseases classified elsewhere	I32	1	0
Acute and subacute endocarditis	I33	4	4
Nonrheumatic mitral valve disorders	I34	2	5
Nonrheumatic aortic valve disorders	I35	6	13
Pulmonary valve disorders	I37	0	1
Endocarditis, valve unspecified	I38	2	4
Acute myocarditis	I40	3	8
Cardiomyopathy	I42	23	9
Cardiomyopathy in diseases classified elsewhere	I43	1	0
Atrioventricular and left bundle-branch block	I44	38	17
Other conduction disorders	I45	8	2
Cardiac arrest	I46	4	6
Paroxysmal tachycardia	I47	42	24
Atrial fibrillation and flutter	I48	91	95
Other cardiac arrhythmias	I49	41	17
Heart failure	I50	78	48
Complications and ill-defined descriptions of heart disease	I51	2	1
Other heart disorders in diseases classified elsewhere	I52	3	0
Subarachnoid haemorrhage	I60	4	4
Intracerebral haemorrhage	I61	5	14
Other nontraumatic intracranial haemorrhage	I62	6	4
Cerebral infarction	I63	51	82
Stroke, not specified as haemorrhage or infarction	I64	2	2
Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	I65	3	7
Other cerebrovascular diseases	I67	8	3
Sequelae of cerebrovascular disease	I69	5	10
Atherosclerosis	I70	8	18
Aortic aneurysm and dissection	I71	8	12
Other aneurysm and dissection	I72	3	4
Other peripheral vascular diseases	I73	4	2
Arterial embolism and thrombosis	I74	4	3
Other disorders of arteries and arterioles	I77	6	0
Phlebitis and thrombophlebitis	I80	18	5

Diagnosis	ICD 10	Cases	Control*
Portal vein thrombosis	I81	1	1
Other venous embolism and thrombosis	I82	2	2
Varicose veins of lower extremities	I83	6	3
Oesophageal varices	I85	2	6
Varicose veins of other sites	I86	0	2
Other disorders of veins	I87	1	1
Nonspecific lymphadenitis	I88	3	1
Other noninfective disorders of lymphatic vessels and lymph nodes	I89	1	4
Hypotension	I95	9	8
Postprocedural disorders of circulatory system, not elsewhere classified	I97	1	0
Other and unspecified disorders of circulatory system	I99	0	1
Acute nasopharyngitis [common cold]	J00	1	0
Acute sinusitis	J01	14	3
Acute pharyngitis	J02	6	3
Acute tonsillitis	J03	9	11
Acute laryngitis and tracheitis	J04	4	1
Acute obstructive laryngitis [croup] and epiglottitis	J05	0	1
Acute upper respiratory infections of multiple and unspecified sites	J06	29	7
Influenza due to certain identified influenza virus	J09	6	4
Influenza due to other identified influenza virus	J10	10	11
Influenza, virus not identified	J11	2	3
Viral pneumonia, not elsewhere classified	J12	2	0
Pneumonia due to Streptococcus pneumoniae	J13	20	16
Pneumonia due to Haemophilus influenzae	J14	20	7
Bacterial pneumonia, not elsewhere classified	J15	74	65
Pneumonia due to other infectious organisms, not elsewhere classified	J16	1	0
Pneumonia, organism unspecified	J18	128	68
Acute bronchitis	J20	12	15
Unspecified acute lower respiratory infection	J22	6	2
Vasomotor and allergic rhinitis	J30	1	0
Chronic sinusitis	J32	9	4
Nasal polyp	J33	6	4
Other disorders of nose and nasal sinuses	J34	2	5
Chronic diseases of tonsils and adenoids	J35	8	9
Peritonsillar abscess	J36	2	8
Chronic laryngitis and laryngotracheitis	J37	1	1
Diseases of vocal cords and larynx, not elsewhere classified	J38	5	2
Other diseases of upper respiratory tract	J39	2	3
Bronchitis, not specified as acute or chronic	J40	4	2
Simple and mucopurulent chronic bronchitis	J41	1	0
Unspecified chronic bronchitis	J42	2	1

Diagnosis	ICD 10	Cases	Control*
Emphysema	J43	1	0
Other chronic obstructive pulmonary disease	J44	24	27
Asthma	J45	14	9
Status asthmaticus	J46	4	4
Bronchiectasis	J47	3	1
Coalworker pneumoconiosis	J60	1	0
Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours	J68	2	0
Pneumonitis due to solids and liquids	J69	5	7
Respiratory conditions due to other external agents	J70	0	1
Adult respiratory distress syndrome	J80	2	0
Pulmonary oedema	J81	4	2
Other interstitial pulmonary diseases	J84	20	1
Abscess of lung and mediastinum	J85	6	1
Pyothorax	J86	3	2
Pleural effusion, not elsewhere classified	J90	19	16
Pneumothorax	J93	23	4
Postprocedural respiratory disorders, not elsewhere classified	J95	1	0
Respiratory failure, not elsewhere classified	J96	23	8
Other respiratory disorders	J98	15	1
Diseases of pulp and periapical tissues	K04	4	1
Gingivitis and periodontal diseases	K05	2	0
Dentofacial anomalies [including malocclusion]	K07	1	2
Other disorders of teeth and supporting structures	K08	1	0
Other diseases of jaws	K10	0	2
Diseases of salivary glands	K11	5	5
Stomatitis and related lesions	K12	1	3
Other diseases of lip and oral mucosa	K13	1	1
Oesophagitis	K20	3	8
Gastro-oesophageal reflux disease	K21	12	6
Other diseases of oesophagus	K22	5	8
Gastric ulcer	K25	5	14
Duodenal ulcer	K26	5	13
Peptic ulcer, site unspecified	K27	0	1
Gastrojejunal ulcer	K28	0	1
Gastritis and duodenitis	K29	13	17
Functional dyspepsia	K30	8	6
Other diseases of stomach and duodenum	K31	6	3
Acute appendicitis	K35	50	67
Other appendicitis	K36	3	2
Unspecified appendicitis	K37	8	11
Other diseases of appendix	K38	2	0
Inguinal hernia	K40	15	16

Diagnosis	ICD 10	Cases	Control*
Femoral hernia	K41	1	0
Umbilical hernia	K42	10	8
Ventral hernia	K43	22	29
Diaphragmatic hernia	K44	4	4
Other abdominal hernia	K45	4	5
Unspecified abdominal hernia	K46	3	0
Crohn disease [regional enteritis]	K50	1	2
Ulcerative colitis	K51	1	2
Other noninfective gastroenteritis and colitis	K52	18	10
Vascular disorders of intestine	K55	3	3
Paralytic ileus and intestinal obstruction without hernia	K56	28	43
Diverticular disease of intestine	K57	38	48
Irritable bowel syndrome	K58	3	3
Other functional intestinal disorders	K59	29	17
Fissure and fistula of anal and rectal regions	K60	3	6
Abscess of anal and rectal regions	K61	15	16
Other diseases of anus and rectum	K62	6	4
Other diseases of intestine	K63	5	5
Haemorrhoids and perianal venous thrombosis	K64	3	6
Peritonitis	K65	6	3
Alcoholic liver disease	K70	3	9
Toxic liver disease	K71	1	1
Hepatic failure, not elsewhere classified	K72	2	9
Chronic hepatitis, not elsewhere classified	K73	1	0
Fibrosis and cirrhosis of liver	K74	5	5
Other inflammatory liver diseases	K75	2	3
Other diseases of liver	K76	6	4
Cholelithiasis	K80	115	110
Cholecystitis	K81	15	19
Other diseases of gallbladder	K82	1	1
Other diseases of biliary tract	K83	7	8
Acute pancreatitis	K85	33	26
Other diseases of pancreas	K86	4	6
Intestinal malabsorption	K90	1	1
Postprocedural disorders of digestive system, not elsewhere classified	K91	4	1
Other diseases of digestive system	K92	17	29
Cutaneous abscess, furuncle and carbuncle	L02	12	12
Cellulitis	L03	9	11
Acute lymphadenitis	L04	1	0
Pilonidal cyst	L05	3	1
Other local infections of skin and subcutaneous tissue	L08	10	7
Atopic dermatitis	L20	1	0

Diagnosis	ICD 10	Cases	Control*
Dermatitis due to substances taken internally	L27	5	0
Pruritus	L29	1	0
Other dermatitis	L30	1	3
Psoriasis	L40	7	0
Urticaria	L50	5	7
Erythema multiforme	L51	1	0
Erythema nodosum	L52	1	0
Other erythematous conditions	L53	1	1
Other follicular disorders	L73	1	0
Decubitus ulcer and pressure area	L89	4	2
Atrophic disorders of skin	L90	2	0
Vasculitis limited to skin, not elsewhere classified	L95	1	0
Ulcer of lower limb, not elsewhere classified	L97	10	1
Other disorders of skin and subcutaneous tissue, not elsewhere classified	L98	6	3
Pyogenic arthritis	M00	7	15
Reactive arthropathies	M02	3	2
Postinfective and reactive arthropathies in diseases classified elsewhere	M03	1	0
Other rheumatoid arthritis	M06	0	1
Gout	M10	6	5
Other crystal arthropathies	M11	1	2
Other arthritis	M13	6	6
Arthropathies in other diseases classified elsewhere	M14	1	0
Polyarthrosis	M15	1	0
Coxarthrosis [arthrosis of hip]	M16	48	81
Gonarthrosis [arthrosis of knee]	M17	56	65
Arthrosis of first carpometacarpal joint	M18	5	6
Other arthrosis	M19	17	23
Acquired deformities of fingers and toes	M20	4	2
Other acquired deformities of limbs	M21	3	9
Disorders of patella	M22	1	1
Internal derangement of knee	M23	2	8
Other specific joint derangements	M24	8	17
Other joint disorders, not elsewhere classified	M25	3	4
Polyarteritis nodosa and related conditions	M30	1	1
Other necrotizing vasculopathies	M31	5	4
Systemic lupus erythematosus	M32	3	3
Dermatopolymyositis	M33	2	0
Systemic sclerosis	M34	1	0
Other systemic involvement of connective tissue	M35	5	4
Kyphosis and lordosis	M40	1	1
Scoliosis	M41	1	0
Other deforming dorsopathies	M43	4	8

Diagnosis	ICD 10	Cases	Control*
Ankylosing spondylitis	M45	1	0
Other inflammatory spondylopathies	M46	5	3
Spondylosis	M47	1	7
Other spondylopathies	M48	36	47
Cervical disc disorders	M50	15	7
Other intervertebral disc disorders	M51	33	42
Other dorsopathies, not elsewhere classified	M53	2	4
Dorsalgia	M54	58	54
Myositis	M60	0	2
Other disorders of muscle	M62	5	4
Synovitis and tenosynovitis	M65	3	6
Spontaneous rupture of synovium and tendon	M66	1	0
Soft tissue disorders related to use, overuse and pressure	M70	4	5
Other bursopathies	M71	1	0
Fibroblastic disorders	M72	4	5
Shoulder lesions	M75	13	19
Enthesopathies of lower limb, excluding foot	M76	2	2
Other enthesopathies	M77	3	2
Other soft tissue disorders, not elsewhere classified	M79	40	43
Osteoporosis with pathological fracture	M80	0	1
Disorders of continuity of bone	M84	5	11
Other disorders of bone density and structure	M85	1	0
Osteomyelitis	M86	6	5
Osteonecrosis	M87	7	8
Other disorders of cartilage	M94	1	0
Other acquired deformities of musculoskeletal system and connective tissue	M95	0	1
Postprocedural musculoskeletal disorders, not elsewhere classified	M96	1	4
Biomechanical lesions, not elsewhere classified	M99	7	7
Acute nephritic syndrome	N00	1	0
Chronic nephritic syndrome	N03	4	3
Nephrotic syndrome	N04	2	3
Unspecified nephritic syndrome	N05	1	1
Acute tubulo-interstitial nephritis	N10	30	45
Chronic tubulo-interstitial nephritis	N11	0	1
Tubulo-interstitial nephritis, not specified as acute or chronic	N12	3	1
Obstructive and reflux uropathy	N13	22	13
Other renal tubulo-interstitial diseases	N15	1	0
Acute renal failure	N17	18	18
Chronic kidney disease	N18	31	20
Unspecified kidney failure	N19	3	3
Calculus of kidney and ureter	N20	66	48
Calculus of lower urinary tract	N21	7	1

Diagnosis	ICD 10	Cases	Control*
Disorders resulting from impaired renal tubular function	N25	1	0
Other disorders of kidney and ureter, not elsewhere classified	N28	1	4
Cystitis	N30	9	9
Neuromuscular dysfunction of bladder, not elsewhere classified	N31	0	3
Other disorders of bladder	N32	3	1
Urethral stricture	N35	5	2
Other disorders of urethra	N36	0	2
Other disorders of urinary system	N39	53	58
Hyperplasia of prostate	N40	11	26
Hydrocele and spermatocele	N43	1	0
Torsion of testis	N44	1	0
Orchitis and epididymitis	N45	4	7
Redundant prepuce, phimosis and paraphimosis	N47	1	0
Other disorders of penis	N48	0	1
Inflammatory disorders of male genital organs, not elsewhere classified	N49	1	1
Hypertrophy of breast	N62	5	5
Salpingitis and oophoritis	N70	2	7
Inflammatory disease of uterus, except cervix	N71	2	1
Other female pelvic inflammatory diseases	N73	0	1
Diseases of Bartholin gland	N75	1	1
Other inflammation of vagina and vulva	N76	0	1
Endometriosis	N80	6	12
Female genital prolapse	N81	19	22
Fistulae involving female genital tract	N82	1	1
Noninflammatory disorders of ovary, fallopian tube and broad ligament	N83	7	6
Polyp of female genital tract	N84	2	1
Other noninflammatory disorders of uterus, except cervix	N85	2	1
Dysplasia of cervix uteri	N87	3	4
Other noninflammatory disorders of cervix uteri	N88	0	1
Other noninflammatory disorders of vagina	N89	3	0
Other noninflammatory disorders of vulva and perineum	N90	0	1
Excessive, frequent and irregular menstruation	N92	15	17
Pain and other conditions associated with female genital organs and menstrual cycle	N94	2	1
Menopausal and other perimenopausal disorders	N95	4	2
Postprocedural disorders of genitourinary system, not elsewhere classified	N99	2	3
Ectopic pregnancy	O00	6	10
Other abnormal products of conception	O02	3	11
Spontaneous abortion	O03	9	12
Medical abortion	O04	0	1
Complications following abortion and ectopic and molar pregnancy	O08	1	0
Pre-existing hypertension complicating pregnancy, childbirth and the puerperium	O10	1	0
Gestational [pregnancy-induced] hypertension	O13	3	5

Diagnosis	ICD 10	Cases	Control*
Pre-eclampsia	O14	3	5
Haemorrhage in early pregnancy	O20	3	0
Excessive vomiting in pregnancy	O21	5	7
Venous complications and haemorrhoids in pregnancy	O22	1	1
Infections of genitourinary tract in pregnancy	O23	2	1
Diabetes mellitus in pregnancy	O24	2	1
Maternal care for other conditions predominantly related to pregnancy	O26	5	8
Multiple gestation	O30	1	0
Maternal care for known or suspected malpresentation of fetus	O32	0	4
Maternal care for other known or suspected fetal problems	O36	0	3
Placenta praevia	O44	0	1
Antepartum haemorrhage, not elsewhere classified	O46	1	5
False labour	O47	10	20
Failed induction of labour	O61	1	0
Postpartum haemorrhage	O72	1	1
Other complications of labour and delivery, not elsewhere classified	O75	0	1
Single spontaneous delivery	O80	201	431
Single delivery by forceps and vacuum extractor	O81	18	42
Single delivery by caesarean section	O82	63	120
Other assisted single delivery	O83	0	1
Multiple delivery	O84	3	10
Puerperal sepsis	O85	1	5
Other puerperal infections	O86	3	2
Obstetric embolism	O88	1	0
Complications of anaesthesia during the puerperium	O89	1	0
Complications of the puerperium, not elsewhere classified	O90	0	1
Infections of breast associated with childbirth	O91	3	4
Other disorders of breast and lactation associated with childbirth	O92	1	1
Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium	O98	1	1
Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium	O99	12	7
Congenital hydrocephalus	Q03	0	1
Spina bifida	Q05	1	0
Other congenital malformations of nervous system	Q07	0	1
Other congenital malformations of eye	Q15	0	1
Other congenital malformations of face and neck	Q18	1	4
Congenital malformations of cardiac septa	Q21	1	3
Congenital malformations of aortic and mitral valves	Q23	0	1
Other congenital malformations of circulatory system	Q28	1	1
Congenital malformations of oesophagus	Q39	1	0
Other congenital malformations of intestine	Q43	0	1

Diagnosis	ICD 10	Cases	Control*
Congenital malformations of gallbladder, bile ducts and liver	Q44	0	1
Cystic kidney disease	Q61	1	2
Congenital ichthyosis	Q80	0	1
Other congenital malformations of skin	Q82	0	1
Congenital malformations of breast	Q83	1	1
Phakomatoses, not elsewhere classified	Q85	0	3
Congenital malformation syndromes due to known exogenous causes, not elsewhere classified	Q86	0	1
Other specified congenital malformation syndromes affecting multiple systems	Q87	0	1
Abnormalities of heart beat	R00	24	24
Haemorrhage from respiratory passages	R04	12	6
Cough	R05	9	1
Abnormalities of breathing	R06	66	26
Pain in throat and chest	R07	175	197
Other symptoms and signs involving the circulatory and respiratory systems	R09	1	5
Abdominal and pelvic pain	R10	129	107
Nausea and vomiting	R11	32	15
Dysphagia	R13	6	6
Faecal incontinence	R15	0	1
Hepatomegaly and splenomegaly, not elsewhere classified	R16	4	0
Unspecified jaundice	R17	3	4
Ascites	R18	5	4
Other symptoms and signs involving the digestive system and abdomen	R19	6	3
Disturbances of skin sensation	R20	25	23
Rash and other nonspecific skin eruption	R21	0	1
Localized swelling, mass and lump of skin and subcutaneous tissue	R22	3	5
Other skin changes	R23	0	1
Abnormal involuntary movements	R25	4	2
Abnormalities of gait and mobility	R26	2	3
Other lack of coordination	R27	1	0
Other symptoms and signs involving the nervous and musculoskeletal systems	R29	6	6
Pain associated with micturition	R30	2	0
Unspecified haematuria	R31	6	4
Unspecified urinary incontinence	R32	0	1
Retention of urine	R33	1	7
Polyuria	R35	2	0
Other symptoms and signs involving the urinary system	R39	1	0
Somnolence, stupor and coma	R40	7	6
Other symptoms and signs involving cognitive functions and awareness	R41	13	9
Dizziness and giddiness	R42	56	68
Other symptoms and signs involving general sensations and perceptions	R44	0	2
Symptoms and signs involving emotional state	R45	1	0
Speech disturbances, not elsewhere classified	R47	0	2

Diagnosis	ICD 10	Cases	Control*
Fever of other and unknown origin	R50	50	32
Headache	R51	39	40
Pain, not elsewhere classified	R52	22	12
Malaise and fatigue	R53	5	15
Syncope and collapse	R55	72	71
Convulsions, not elsewhere classified	R56	26	33
Shock, not elsewhere classified	R57	2	1
Haemorrhage, not elsewhere classified	R58	0	2
Enlarged lymph nodes	R59	55	1
Oedema, not elsewhere classified	R60	10	4
Symptoms and signs concerning food and fluid intake	R63	4	4
Cachexia	R64	1	0
Unknown and unspecified causes of morbidity	R69	0	1
Elevated erythrocyte sedimentation rate and abnormality of plasma viscosity	R70	2	0
Elevated blood glucose level	R73	7	4
Abnormal serum enzyme levels	R74	2	3
Other abnormal findings of blood chemistry	R79	3	2
Isolated proteinuria	R80	0	1
Abnormal findings on diagnostic imaging of central nervous system	R90	2	1
Abnormal findings on diagnostic imaging of lung	R91	31	7
Abnormal findings on diagnostic imaging of other body structures	R93	5	4
Abnormal results of function studies	R94	6	0
Superficial injury of head	S00	7	8
Open wound of head	S01	4	9
Fracture of skull and facial bones	S02	14	12
Dislocation, sprain and strain of joints and ligaments of head	S03	1	0
Injury of eye and orbit	S05	0	1
Intracranial injury	S06	36	42
Other and unspecified injuries of head	S09	2	0
Superficial injury of neck	S10	1	3
Open wound of neck	S11	1	0
Fracture of neck	S12	4	7
Dislocation, sprain and strain of joints and ligaments at neck level	S13	4	1
Injury of nerves and spinal cord at neck level	S14	0	2
Crushing injury of neck	S17	0	1
Traumatic amputation at neck level	S18	1	0
Superficial injury of thorax	S20	8	3
Fracture of rib(s), sternum and thoracic spine	S22	14	26
Dislocation, sprain and strain of joints and ligaments of thorax	S23	0	1
Injury of nerves and spinal cord at thorax level	S24	0	1
Injury of heart	S26	1	0
Injury of other and unspecified intrathoracic organs	S27	6	8

Diagnosis	ICD 10	Cases	Control*
Superficial injury of abdomen, lower back and pelvis	S30	3	6
Open wound of abdomen, lower back and pelvis	S31	1	1
Fracture of lumbar spine and pelvis	S32	6	16
Dislocation, sprain and strain of joints and ligaments of lumbar spine and pelvis	S33	0	2
Injury of intra-abdominal organs	S36	0	1
Injury of urinary and pelvic organs	S37	2	2
Superficial injury of shoulder and upper arm	S40	2	1
Open wound of shoulder and upper arm	S41	2	0
Fracture of shoulder and upper arm	S42	29	46
Dislocation, sprain and strain of joints and ligaments of shoulder girdle	S43	3	3
Injury of muscle and tendon at shoulder and upper arm level	S46	5	9
Open wound of forearm	S51	2	1
Fracture of forearm	S52	16	26
Dislocation, sprain and strain of joints and ligaments of elbow	S53	1	4
Injury of nerves at forearm level	S54	1	1
Superficial injury of wrist and hand	S60	0	3
Open wound of wrist and hand	S61	4	3
Fracture at wrist and hand level	S62	7	13
Dislocation, sprain and strain of joints and ligaments at wrist and hand level	S63	2	3
Injury of nerves at wrist and hand level	S64	2	1
Injury of muscle and tendon at wrist and hand level	S66	5	8
Traumatic amputation of wrist and hand	S68	2	2
Superficial injury of hip and thigh	S70	4	3
Open wound of hip and thigh	S71	0	1
Fracture of femur	S72	28	28
Dislocation, sprain and strain of joint and ligaments of hip	S73	1	0
Injury of muscle and tendon at hip and thigh level	S76	7	6
Superficial injury of lower leg	S80	3	3
Open wound of lower leg	S81	2	1
Fracture of lower leg, including ankle	S82	54	81
Dislocation, sprain and strain of joints and ligaments of knee	S83	4	7
Injury of nerves at lower leg level	S84	1	0
Injury of blood vessels at lower leg level	S85	1	0
Injury of muscle and tendon at lower leg level	S86	2	9
Superficial injury of ankle and foot	S90	0	2
Open wound of ankle and foot	S91	0	2
Fracture of foot, except ankle	S92	6	6
Dislocation, sprain and strain of joints and ligaments at ankle and foot level	S93	3	1
Injury of muscle and tendon at ankle and foot level	S96	1	0
Superficial injuries involving multiple body regions	T00	1	0
Fractures involving multiple body regions	T02	0	1
Crushing injuries involving multiple body regions	T04	0	1

Diagnosis	ICD 10	Cases	Control*
Unspecified multiple injuries	T07	0	1
Injury of unspecified body region	T14	2	2
Foreign body in respiratory tract	T17	3	0
Foreign body in alimentary tract	T18	4	8
Foreign body in genitourinary tract	T19	0	2
Burn and corrosion of head and neck	T20	0	3
Burn and corrosion of trunk	T21	1	0
Burn and corrosion of wrist and hand	T23	1	0
Burn and corrosion of ankle and foot	T25	0	2
Burn and corrosion of respiratory tract	T27	0	1
Burns classified according to extent of body surface involved	T31	0	2
Frostbite involving multiple body regions and unspecified frostbite	T35	0	1
Poisoning by hormones and their synthetic substitutes and antagonists, not elsewhere classified	T38	0	1
Poisoning by nonopioid analgesics, antipyretics and antirheumatics	T39	1	1
Poisoning by narcotics and psychodysleptics [hallucinogens]	T40	3	2
Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs	T42	6	6
Poisoning by psychotropic drugs, not elsewhere classified	T43	2	1
Poisoning by agents primarily affecting the cardiovascular system	T46	0	1
Poisoning by diuretics and other and unspecified drugs, medicaments and biological substances	T50	28	40
Toxic effect of alcohol	T51	6	6
Toxic effect of organic solvents	T52	0	1
Toxic effect of carbon monoxide	T58	1	0
Toxic effect of other gases, fumes and vapours	T59	3	2
Toxic effect of contact with venomous animals	T63	2	4
Toxic effect of other and unspecified substances	T65	0	3
Unspecified effects of radiation	T66	1	0
Effects of heat and light	T67	1	0
Asphyxiation	T71	0	2
Effects of other external causes	T75	0	1
Adverse effects, not elsewhere classified	T78	16	20
Certain early complications of trauma, not elsewhere classified	T79	5	5
Complications following infusion, transfusion and therapeutic injection	T80	0	2
Complications of procedures, not elsewhere classified	T81	74	70
Complications of cardiac and vascular prosthetic devices, implants and grafts	T82	6	8
Complications of genitourinary prosthetic devices, implants and grafts	T83	7	6
Complications of internal orthopaedic prosthetic devices, implants and grafts	T84	22	23
Complications of other internal prosthetic devices, implants and grafts	T85	8	4
Failure and rejection of transplanted organs and tissues	T86	4	3
Complications peculiar to reattachment and amputation	T87	1	0
Other complications of surgical and medical care, not elsewhere classified	T88	16	8
Sequelae of injuries of neck and trunk	T91	2	0
Sequelae of injuries of upper limb	T92	5	8

Diagnosis	ICD 10	Cases	Control*
Sequelae of injuries of lower limb	T93	1	2
Sequelae of injuries involving multiple and unspecified body regions	T94	1	0
Sequelae of burns, corrosions and frostbite	T95	0	1
General examination and investigation of persons without complaint and reported diagnosis	Z00	3	13
Other special examinations and investigations of persons without complaint or reported diagnosis	Z01	4	2
Medical observation and evaluation for suspected diseases and conditions	Z03	112	95
Examination and observation for other reasons	Z04	6	10
Follow-up examination after treatment for malignant neoplasms	Z08	3	2
Follow-up examination after treatment for conditions other than malignant neoplasms	Z09	7	2
Special screening examination for other diseases and disorders	Z13	1	0
Carrier of infectious disease	Z22	1	0
Need for other prophylactic measures	Z29	4	3
Contraceptive management	Z30	1	2
Pregnancy examination and test	Z32	1	0
Supervision of normal pregnancy	Z34	2	4
Supervision of high-risk pregnancy	Z35	1	2
Outcome of delivery	Z37	0	1
Postpartum care and examination	Z39	2	7
Prophylactic surgery	Z40	2	2
Procedures for purposes other than remedying health state	Z41	4	3
Follow-up care involving plastic surgery	Z42	16	15
Attention to artificial openings	Z43	6	5
Fitting and adjustment of external prosthetic device	Z44	1	0
Adjustment and management of implanted device	Z45	15	6
Fitting and adjustment of other devices	Z46	3	2
Other orthopaedic follow-up care	Z47	10	8
Other surgical follow-up care	Z48	27	39
Care involving dialysis	Z49	3	6
Care involving use of rehabilitation procedures	Z50	2	0
Other medical care	Z51	52	36
Donors of organs and tissues	Z52	1	2
Persons encountering health services for specific procedures, not carried out	Z53	6	4
Problems related to social environment	Z60	0	2
Other problems related to primary support group, including family circumstances	Z63	1	0
Persons encountering health services for other counselling and medical advice, not elsewhere classified	Z71	3	3
Problems related to medical facilities and other health care	Z75	2	1
Persons encountering health services in other circumstances	Z76	0	1
Family history of malignant neoplasm	Z80	1	0
Personal history of malignant neoplasm	Z85	4	5
Personal history of certain other diseases	Z86	1	0

Diagnosis	ICD 10	Cases	Control*
Personal history of other diseases and conditions	Z87	2	0
Acquired absence of limb	Z89	1	0
Personal history of risk-factors, not elsewhere classified	Z91	1	0
Personal history of medical treatment	Z92	1	0
Artificial opening status	Z93	0	2
Transplanted organ and tissue status	Z94	17	1
Presence of cardiac and vascular implants and grafts	Z95	4	2
Presence of other functional implants	Z96	1	0
Other postsurgical states	Z98	4	1

*Two matched controls for each case

Supplement Table 2. Numbers of Visits to Inpatient Care for the major diseases found, where Sarcoid Cases and Matched Controls are compared using Cox Regression.

Diagnosis	ICD10	Case events	Case rate	Controls events	Controls rate	HR	CI
Malignant neoplasms of ill-defined, other secondary and unspecified sites	C76-C80	51	1.29	43	0.54	2.38	1.59 - 3.57
Malignant neoplasms of lymphoid, hematopoietic and related tissue	C81-C96	44	1.12	30	0.38	2.94	1.85 - 4.68
Pulmonary embolism	I26	52	1.32	24	0.30	4.36	2.69 - 7.07
Cardiomyopathy	I42	23	0.58	9	0.11	5.13	2.37 - 11.08
Paroxysmal tachycardia	I47	42	1.07	24	0.30	3.51	2.13 - 5.80
Heart failure	I50	78	1.99	48	0.61	3.27	2.28 - 4.68
Pneumothorax	J93	23	0.58	4	0.05	11.53	3.99 - 33.34
Influenza and pneumonia	J09-J18	215	5.54	146	1.86	2.98	2.41 - 3.68
Chronic lower respiratory diseases	J40-J47	49	1.25	39	0.49	2.53	1.66 - 3.85
Other respiratory diseases principally affecting the interstitium	J80-J84	26	0.66	3	0.04	17.38	5.26 - 57.42

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (1); 136-147 DOI: 10.36141/svdld.v37i1.8461

Treatment of primary sjögren's syndrome-related interstitial lung disease: a retrospective cohort study

Barkha Amlani[1], Ghada Elsayed[2], Umang Barvalia[3], Jeffrey P Kanne[4], Keith C Meyer[5], Nathan Sandbo[5], Zhanhai Li [6], Sara S McCoy[7]

[1] Division of Rheumatology, Department of Internal Medicine Santa Clara Valley Medical Center, San Jose, CA; [2] Rheumatology, Proclinic Center, Cairo, Egypt; [3] Division of Pulmonary & Critical Care, Department of Internal Medicine, Santa Clara Valley Medical Center, San Jose, CA; [4] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI; [5] Division of Pulmonary & Critical Care, Department of Internal Medicine, University of Wisconsin School of Public Health, Madison, WI, 53705, U.S.A; [6] Department of Biostatistics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [7] Division of Rheumatology, Department of Internal Medicine, University of Wisconsin School of Public Health, Madison, WI;

Abstract. *Background:* Interstitial lung disease (ILD) is a common complication of primary Sjögren's syndrome (pSS). Because there is a paucity of literature on the management of pSS-associated ILD (pSS-ILD), this retrospective cohort study assessed the efficacy of azathioprine and mycophenolate therapy in adult patients with pSS-ILD. *Methods:* A retrospective cohort study was performed using electronic health records to identify adults meeting the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for pSS. The presence of pSS-ILD was confirmed by characteristic high-resolution computed tomography and/or histopathology findings. Sociodemographic, clinical, and pulmonary function test (PFT) data were abstracted for patients meeting the criteria and followed longitudinally from the date of their ILD diagnosis. PFT values were anchored on time of treatment start, and linear mixed-effects modeling was used to analyze changes in diffusion capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) before and after treatment initiation. *Results:* We identified 19 subjects who had pSS-ILD, of whom seven were treated with azathioprine and seven were treated with mycophenolate. Within the azathioprine treated group, FVC% slope change trended toward improvement from a rate of -9.8% per month pre-treatment to 2.1% per month post-treatment (p = 0.13). Within the mycophenolate treated group, FVC% slope change improved from a rate of 1.5% per month pre-treatment to 4.3% per month post-treatment (p = 0.02) and DLCO% slope changed from a rate of -3.8% to −1.3% per month (p = 0.01) after therapy start. *Conclusions:* Mycophenolate treatment was associated with significant improvement in PFTs of pSS-ILD patients over time, and azathioprine treatment followed a similar non-significanttrend. Additional prospective studies are needed to further evaluate these findings. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 136-147)*

Key words: Sjögren's Syndrome, Interstitial Lung Disease, Treatment

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Correspondence: Sara McCoy, MD
University of Wisconsin
School of Medicine and Public Health
1685 Highland Avenue
Madison, WI 53705-2281
ssmccoy@medicine.wisc.edu
Email: ssmccoy @medicine.wisc.edu
Phone: (608) 262-0908
Fax: (608) 263-7353

Introduction

Primary Sjögren's syndrome (pSS), a chronic, multisystem autoimmune disease, is characterized by focal lymphocytic infiltration of the lacrimal and salivary glands resulting in dry eyes and dry mouth (1-3). As the second most common multisystem rheumatologic disease, pSS has an estimated incidence between 0.1-0.5% of the general population (1, 4). Systemic involvement is common and can be the initial manifestation of pSS (1, 5). Interstitial lung disease (ILD) is a life-threatening systemic complication of pSS; patients with ILD have a higher mortality than those without ILD (3, 6, 7). Pulmonary involvement is common in pSS, and at least 9-20% of pSS patients have lung involvement (1, 8), with some studies suggesting much higher rates (3, 8, 9). Finally, ILD can precede the diagnosis of pSS in up to 25% of patients (8).

Azathioprine and mycophenolate are commonly utilized for treatment of pSS-ILD. Despite the common use of azathioprine for pSS-ILD, there is only one study (n = 13 patients) that evaluated the effect of azathioprine on lung function in a well-defined cohort of patients with pSS-ILD, and this study did not evaluate differential longitudinal trends in pulmonary function test (PFT) pre- and post-therapy (10). No studies exist that have evaluated the effect of mycophenolate in a well-defined cohort of patients with pSS-ILD. Other studies evaluating azathioprine or mycophenolate in larger mixed cohorts of patients with connective-tissue disease associated ILD had small percentages of pSS patients, and therapeutic effect was not reported for pSS (11, 12). Thus, despite the high frequency and morbidity of pSS-ILD, the effectiveness and safety of commonly utilized immunosuppressive treatments for pSS-ILD remains unknown. This lack of an evidential base to inform the choice of treatment in pSS-ILD creates uncertainty in clinical decision making and potentially delays the initiation of efficacious treatments.

To address this gap in knowledge, we hypothesized that treatment with azathioprine or mycophenolate, with or without rituximab, would attenuate PFT decline over time. To test this hypothesis, we retrospectively analyzed a well-defined cohort of patients with pSS-ILD to evaluate the effect of initiation of azathioprine and mycophenolate on lung function decline. In this manuscript we describe the characteristics of this cohort and report the longitudinal change in PFTs before and after initiation of therapy.

Materials and Methods

Inclusion/exclusion

This study was performed in accordance with the Declaration of Helsinki and approved by the UW Health Sciences Institutional Review Board (IRB) (2013-1121) with a waiver of individual informed consent due to the minimal risk represented by this retrospective study. This is a retrospective cohort study of adults ≥ 18 years old with pSS complicated by ILD. We used the electronic health record (EHR) from an academic health system to create this cohort. Patients were identified who had both CD9/10 codes for pSS and ii) and a diagnosis of ILD. Specific ILD types were identified as nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphoid interstitial pneumonia (LIP), diffuse alveolar damage, or organizing pneumonia (OP). Patients were included if they were evaluated by both pulmonology and rheumatology within our health care system and had clinically confirmed pSS (Figure 1). Records were individually reviewed by a board certified (SM) rheumatologist to ensure each patient met the 2016 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria for pSS (13). Patients with another autoimmune condition in addition to pSS were excluded so that we only included patients who had pSS. The diagnosis of ILD was confirmed either by the presence of characteristic changes on high resolution computed tomography (HRCT), as determined by a thoracic radiologist (J.K), or by characteristic findings of ILD on lung specimen histopathology at the time of diagnosis. Medical records were manually abstracted by MD reviewers (B.A., U.B., and G.A.) for all clinical and serologic data using a standardized case review tool.

Outcome/data collection

Our primary outcome of interest was a significant change in percent predicted forced vital capacity (FVC%) and percent predicted diffusing capacity of carbon-monoxide (DLCO%) between pre- and post-treatment slope determined by linear effects models.

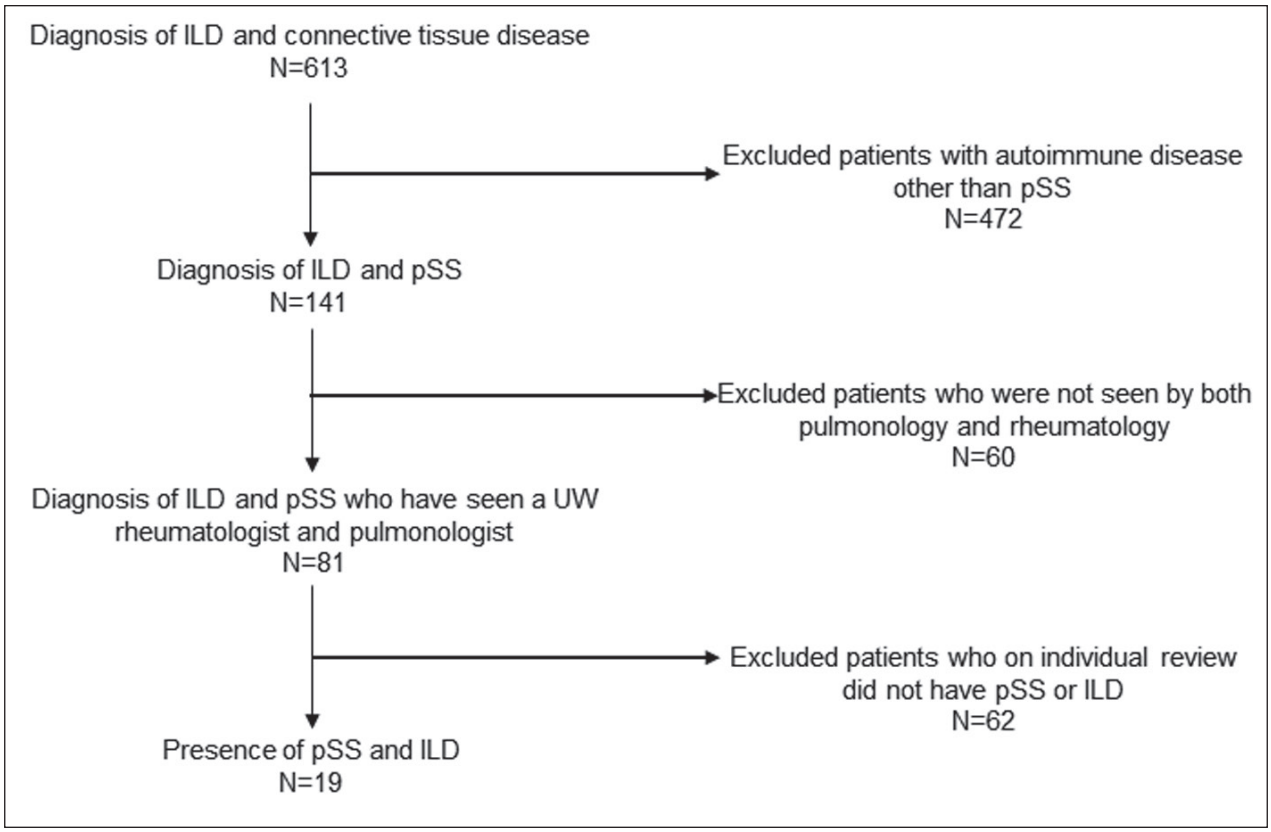

Fig. 1. Cohort flow diagram demonstrating exclusion and inclusion of patients who meet criteria for primary Sjögren's Syndrome (pSS) and interstitial lung disease (ILD) diagnosis and who have seen both pulmonology and rheumatology within the UW health system.

Available PFT data were collected for all patients, averaged in 3-month time intervals, and anchored with the values (T_0) for each patient just prior to the date on which treatment with azathioprine or mycophenolate was initiated. For the grouped analysis, if patients were treated with more than one medication, T_0 was anchored on the start date of the first of the combined treatments. Analysis of the untreated group was anchored with T_0 on date of ILD diagnosis. All HRCT scans were reviewed by a subspecialist thoracic radiologist (J.K.), and morphologic patterns were determined (NSIP, OP, NSIP with OP overlap, LIP, other) according to radiographic patterns.

Variable definitions

Our primary exposures of interest included azathioprine, mycophenolate, and rituximab. Mycophenolic acid was considered equivalent to mycophenolate mofetil for the purposes of this study. Exposure start and end dates were recorded using manual review of EHR prescription data. Sensitivity analysis analyzed treated UIP patients versus a composite of other treated patients. The composite group was composed of diagnoses including NSIP, LIP, and OP.

Additional clinical data abstracted included age, sex, tobacco use, cardiovascular disease (CVD) (defined as coronary artery disease, congestive heart failure, or cerebrovascular disease), gastroesophageal reflux (GERD), obstructive sleep apnea (OSA), malignancy, pulmonary arterial hypertension (PAH), and pulmonary embolism (PE). Clinical features abstracted included pulmonary symptoms at ILD diagnosis, constitutional symptoms, lymphadenopathy, glandular swelling, inflammatory arthritis, cutaneous manifestations of pSS, renal involvement with pSS, muscular involvement with pSS, peripheral or central nervous system manifestations of pSS, immunosuppressive/immunomodulatory therapy, and adverse effects of azathioprine, mycophenolate, or rituximab. Laboratory data on pSS and pSS disease activity were also collected.

Statistical methods

Baseline characteristics between treated group and untreated group were compared with chi-squared test or Fisher's exact test for categorical variables and t-tests for continuous variables. Within the treated group, linear mixed-effects models were used to evaluate for change in PFT slopes (FVC% and DLCO%) per month before and after therapy. Analysis was performed for each treatment group (azathioprine, mycophenolate, and rituximab) as well as for the entire treated cohort. When the entire cohort was evaluated, patients who were treated sequentially with multiple drugs were anchored at the start time of the initial drug. Plots were created illustrating PFTs two years pre- and post-therapy. Pre-treatment PFT slope was projected into the post-treatment portion of the graph for visual comparison of slope change. A p value of < 0.05 was considered to be significant. Statistical analyses were performed using SAS 9.4 (Cary, NC) and GraphPad Prism software (GraphPad Software, La Jolla, CA, USA).

Results

Study population and baseline characteristics

613 patients with ILD and sicca symptoms were identified. 472 patients carried diagnoses of other autoimmune diseases and were excluded (Figure 1). Patients not seen by both pulmonology and rheumatology consultants were also excluded to allow for accurate diagnosis and longitudinal PFT follow-up. After individual chart review, 19 patients with ILD who met the 2016 ACR/EULAR criteria for pSS were identified and comprised our study cohort.

Demographics and clinical characteristics were similar between the treatment groups (Table 1). The mean age for patients who received immunosuppressive treatment was 58 (± 11) years, and the mean age for patients who received no immunosuppressive therapy was 70 (± 11) years.

Symptoms including cough, dyspnea, dry eyes or mouth, joint pain and other constitutional symptoms did not vary significantly between treated versus untreated groups. Other clinical characteristics including cryoglobulinemia, anemia, cytopenia, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), low complement, presence of RF, anti-SSA antibody, anti-Jo1 antibody, anti-neutrophil cytoplasmic antibody (ANCA), anti-ribonucleoprotein (anti-RNP) antibody, anti-Smith antibody, lymphadenopathy, CVD, GERD, malignancy, OSA and PE were similar between the groups (Table 1).

The number of patients treated with azathioprine (n = 7), mycophenolate (n = 7), rituximab (n = 6), or untreated (n = 5) were similar. Indications for treatment initiation were functional decline combined with worsening HRCT or PFTs. The reasoning for therapy choice was explained in three patients. Two patients were started on rituximab for concomitant arthralgias and one was started on rituximab over azathioprine or mycophenolate due to the general increased risk of lymphoma in pSS. Otherwise, no explicit reasoning was provided for the choice of therapy. Five out of six patients who received rituximab also received azathioprine or mycophenolate, one of whom received all three treatments. Of the five patients who received combined therapy, two patients were started on mycophenolate for ILD and rituximab was ultimately added for progression of ILD. A third patient started rituximab initially for ILD and mycophenolate was added for progression of ILD. A fourth patient started azathioprine for ILD and rituximab was added for arthralgias. A fifth patient started mycophenolate for ILD, mycophenolate was stopped and rituximab was started for pSS-related inflammatory myositis. Azathioprine was ultimately added as a steroid sparing agent after an initial rituximab course.

The number of patients receiving hydroxychloroquine, leflunomide, and methotrexate were similar between the groups. The mean dose of azathioprine was 150 mg daily with duration of therapy ranging from three to thirteen years with mean of 7 years. The mean dose used for mycophenolate was 2000 mg daily with duration of therapy ranging from six months to five years with mean of 2 years. The average latency period from ILD diagnosis to the initiation of immunosuppressant therapy did not vary significantly between the three groups but the azathioprine group trended to shorter treatment latency. Between the four groups, there was no significant difference between duration of high dose prednisone use (months ≥ 40 mg), pre-immunosuppression prednisone dose or duration, six month post-immunosuppression prednisone dose or duration, or median prednisone

maintenance dose. The average dose of prednisone before azathioprine start was 9 (± 10) mg and after 6 months of therapy was 6 (±8) mg (p = 0.3). The average dose of prednisone before mycophenolate start was 32 (±26) mg and after 6 months of therapy was 19 mg (±9) (p = 0.03).

Baseline PFTs including FEV1%, FVC%, FEV1/FVC% and DLCO% and baseline oxygen use were similar between the four groups (Table 1). The mean FVC% and DLCO% for five patients in the untreated group was 67% and 39% respectively. Baseline 6-minute walk tests varied between groups but were only reported in two patients each in the azathioprine and mycophenolate groups and in one patient in each of the rituximab and untreated

Table 1. Demographics and Patient Characteristics

	AZA (n=7)	Msg	MMF (n=7)	Msg	Ritux (n=6)	Msg	No Therapy (n=5)	Msg
Mean Age (± SD)	57.7 ± 14.2		58.9 ± 10.6		55.7 ± 10.1		69.6 ± 11.3	
Demographics n(%)								
Alive	6 (86)		5 (71)		5 (83)		2 (40)	
Caucasian	6 (100)	1	6 (100)	1	5 (100)	1	1 (100)	4
Female	6 (86)		5 (83)		5 (83)		5 (100)	
Tobacco ever*	1 (17)	1	5(71)		4 (67)		3 (75)	
Labs n(%)								
ANA positive	6 (86)		6 (86)		6 (100)		4 (100)	1
ANA Titer≥1:320	3 (60)	2	5 (83)	1	4 (67)		4 (100)	1
Nucleolar	1(20)	2	1 (14)	1	1 (17)		0 (0)	1
Speckled	2(40)	2	5 (71)	1	4 (67)		3 (75)	1
Other	2(40)	2	1 (14)	1	1 (17)		1 (25)	1
Cryoglobulinemia	0 (0)	4	0 (0)	3	0 (0)	4	1 (33)	1
Elevated CRP	3 (50)	1	3 (43)		2 (33)		2 (50)	1
Elevated ESR	7 (100)		5 (83)	1	5(83)		2 (50)	1
Low C3/C4	0 (0)		1 (14)		0 (0)		1 (33)	2
RF	3 (50)	1	4 (57)		3 (50)		2 (50)	1
SSA	6 (86)		6 (86)		5 (83)		3 (75)	1
Comorbidities n(%)								
#CVD	1 (17)		1 (17)		1 (25)	2	1 (25)	1
GERD	5 (71)		7 (100)		4 (67)		4 (100)	1
Malignancy	2 (33)	1	0 (0)	2	0 (0)	2	1 (25)	1
OSA	2 (33)	1	1 (20)	1	1 (25)	2	1 (33)	2
PE	1 (17)		1 (20)	1	1 (25)	2	0 (0)	
PAH	1 (17)		3 (50)		2 (50)	2	2 (67)	2
Diagnosis to IS start (Months ± SD)	4.3 ± 6.4		29.1 ± 46.7		44.4 ± 9.6	1	N/A	
Treatment n(%)								
HCQ	5 (71)		5 (71)		5 (83)		1 (25)	1
Leflunomide	1 (14)		1 (14)		1 (17)		0 (0)	

	AZA (n=7)	Msg	MMF (n=7)	Msg	Ritux (n=6)	Msg	No Therapy (n=5)	Msg
MTX	1 (14)		1 (14)		1 (17)		0 (0)	
Prednisone	4 (57)		7 (100)		5 (83)		2 (40)	
Duration prednisone ≥40 mg (months ± SD)	0.5 ± 0.55	1	1.3 ± 2.05		0.7 ± 0.8		0.5 ± 0.6	
Duration prednisone pre-IS (months ± SD)	3.8 ± 4.6	1	4.2 ± 4.4		7.3 ± 5.5		N/A	
Dose prednisone pre-IS (mg ± SD)	9.2 ± 10.2	1	31.7 ± 25.6		23.3 ± 15.1		N/A	3
Duration prednisone post-IS (months ± SD)	45.6 ± 69.1	1	22.3 ± 22.7		26.4 ± 32.4		N/A	
Dose prednisone 6 months post-IS (mg ± SD)	6.3 ± 7.5	1	19 ± 8.9		12.1 ± 7.5	1	0.8 ± 2.0	
Median prednisone maintenance dose* (mg ± SD)	2.5 ± 2.7	1	12.9 ± 10.8		7.5 ± 6.9		0.8 ± 2.0	
Baseline PFTs (% ± SD)								
FEV1%	84 ± 2.9		70 ± 11.7	2	70 ± 19.6	3	59 ± 14.6	3
FVC%	86 ± 26.0		64 ± 7.9	1	74 ± 15.5	2	67 ± 17.9	2
FEV1/FVC%	88 ± 15.9	3	88 ± 7.0	3	91 ± 11.7	3	73 ± 14.7	2
DLCO%	57 ± 23.6		45 ± 9.1	1	59 ± 14.84	2	39 ± 16.0	4
Baseline 6MWT distance (feet ± SD)*	993 ± 151	5	1267 ± 208	5	1119 ± 0	5	450 ± 0	4
Oxygen at baseline n(%)	1 (17)		3 (43)		1 (17)		0	
BAL n(%)								
+Eosinophilic	0 (0)	3	1 (50)	5	0 (0)	4	0 (0)	2
^Lymphocytic	2 (50)	3	1 (50)	5	2 (100)	4	1 (33)	2
Normal	2 (50)	3	0 (0)	5	0 (0)	4	2 (67)	2
HRCT pattern n(%)								
LIP	4 (57)		1 (14)		2 (33)		1 (25)	1
NSIP	1 (14)		5 (71)		3 (50)		1 (25)	1
OP	1 (14)		0 (0)		0 (0)		0 (0)	1
UIP	0 (0)		0 (0)		0 (0)		0 (0)	1
Other	1 (14)		1 (14)		1 (17)		2 (50)	1
Lung biopsy n(%)								
LIP	2 (33)	1	1 (20)	2	2 (50)	2	0 (0)	3
NSIP	1 (17)	1	3 (60)	2	1 (25)	2	0 (0)	3
UIP	1 (17)	1	1 (20)	2	1 (25)	2	0 (0)	3
Other	2 (33)	1	0 (0)	2	0 (0)	2	2 (100)	3

AZA: Azathioprine; MMF: Mycophenolate; Ritux: Rituximab; SD: Standard deviation; *p < 0.05; ANA: Antinuclear antibody; CVD: Cardiovascular disease; #CVD history includes coronary artery disease, congestive heart failure, or cerebrovascular event; GERD: Gastroesophageal reflux disease; OSA: Obstructive sleep apnea; PE: Pulmonary embolism; PAH: Pulmonary arterial hypertension; HCQ: Hydroxychloroquine; MTX: Methotrexate; IS: immunosuppression; 6MWT: 6-Minute Walk Test; BAL: Bronchoalveolar lavage; +≥2% eosinophilic; ^≥15% lymphocytic; HRCT: High resolution computed tomography LIP: Lymphoid interstitial pneumonia; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; UIP: Usual interstitial pneumonia

groups. Oxygen use was similar between these groups at baseline.

Imaging, biopsy, and bronchoalveolar lavage

Patients in azathioprine treatment group predominantly had a LIP pattern (n = 4) compared to the mycophenolate treated group, which predominantly had a NSIP pattern (n = 5). The untreated group included one patient with LIP and one patient with NSIP. The differences were not statistically significant. None of the patients in either treatment group had a UIP pattern on HRCT. Two patients had changes consistent with significant aspiration on HRCT.

Histopathology results for 13 patients who had undergone native lung biopsy were available. The different patterns of involvement are included in Table 1. Additional findings included chronic bronchiolitis (n = 2) and hypersensitivity pneumonia (n = 1). Six patients did not have a biopsy despite imaging consistent with ILD. Of the four HRCT-diagnosed NSIP patients who did not receive biopsy, three were untreated and one was treated with mycophenolate. Biopsy was not performed in one untreated patient because the ILD was mild and stable. One patient with NSIP on HRCT was not biopsied due to presentation with severe exacerbation and was considered too high risk for biopsy before their ultimate death. Two cases of NSIP were not biopsied and no justification was provided. Of the two patients with HRCT-diagnosed LIP without histopathologic confirmation, one patient was in the untreated group and one patient was treated with azathioprine. The two patients with LIP were not biopsied because their clinical course was stable.

Bronchoalveolar lavage (BAL) results from 11 patients showed a majority of patients (n = 5) with lymphocytosis (≥15% lymphocytes). Four patients had a normal BAL nucleated immune cell profile, one had BAL that showed an increase in eosinophils, and one had a contaminated sample with numerous squamous epithelial cells.

Adverse effects of therapy

Azathioprine was discontinued in one patient after ten years of use because of recurrent uncomplicated lower urinary tract infections. Azathioprine was stopped in another patient after three years out of concern for bleeding risk when the patient presented with uncomplicated rectal bleeding. One patient was switched from mycophenolate to azathioprine because of an ILD exacerbation. One NSIP patient on mycophenolate developed respiratory failure secondary to rhinovirus infection and died. One LIP patient who received mycophenolate and one dose of rituximab died while in hospice care for ILD symptoms. One patient had mild neutropenia due to mycophenolate (lowest 1.95 K/μL; normal 2.3-8.6 K/μL). without and associated infections. The cause of death was unknown for two patients (one who was receiving azathioprine and the other was not on treatment). No patients had liver enzyme elevation.

Regarding malignancies, one patient developed mucosa-associated lymphoid tissue (MALT) lymphoma of the lung 12 years after azathioprine was discontinued. This patient had a biopsy at the time of the initial diagnosis that showed LIP and repeat lung biopsy twelve years later diagnosed MALT lymphoma. One untreatated patient developed MALT lymphoma of the parotid gland. This patient did not have a lung biopsy. Finally, one patient had uterine cancer decades before development and treatment of ILD.

Pulmonary Function Tests

Azathioprine Group

The slope of FVC% trended toward improvement after azathioprine treatment (Figure 2A). The FVC% slope for patients in azathioprine group before treatment was increasing at a rate of 2% per month and after treatment was increasing at a rate of 4% per month (p = 0.13) (Table 2). The mean FVC% before treatment in the azathioprine group was 72% and the mean FVC% after treatment was 76%. Only one patient had a recorded DLCO% before treatment in the azathioprine group so evaluation of DLCO% in this group was limited (Figure 2B, Table 2).

Mycophenolate Group

The change in slope of FVC% before and after mycophenolate therapy significantly improved after treatment. The change in FVC% slope was declining at a rate of -10% per month before therapy, and after therapy the slope improved to a rate of 2% per month (p = 0.02) (Figure 3A, Table 2).

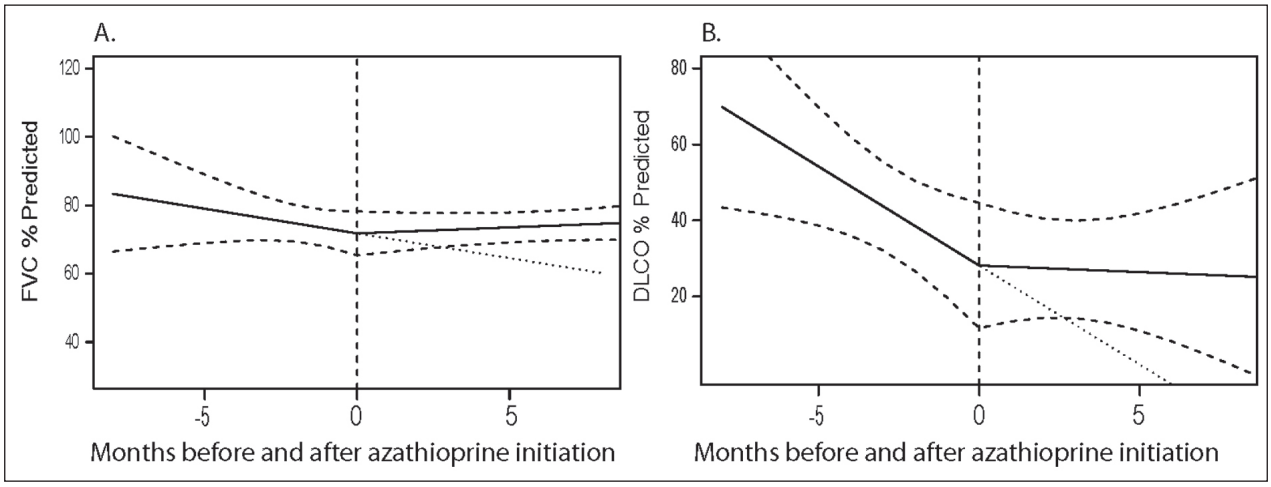

Fig. 2. Mixed-effects model estimate of FVC% and DLCO% slope before and after initiation of azathioprine plotted 12 months before and 12 months after azathioprine start. The bold perforated line represents the 95% confidence interval. The light perforated line represents the trajectory of the pre-treatment slope. (a) FVC% slope before treatment was declining at a rate of 1.5% per month and after treatment was increasing at a rate of 4.3% per month (p=0.13); (b) DLCO% slope after treatment was declining at a rate of -0.3% per month (p=0.96).

Table 2. FVC% and DLCO% Before and After Azathioprine and Mycophenolate Treatment

	AZA			MMF		
	Before IS	**After IS**	**P value**	**Before IS**	**After IS**	**P value**
FVC%						
Mean	71.9	75.7	0.46	54.9	60.5	0.34
Slope Change	1.5 ± 11.4	4.3 ± 7.6	0.13	-9.8 ± 11.7	2.1 ± 7.7	0.02
DLCO%						
Mean	47.3	28.7	0.17	45.2	41.6	0.59
Slope Change	0	-0.3 ± 4.5	0.96	-3.8 ± 3.7	-1.3 ± 3.2	0.01

FVC% and DLCO% mean included mean PFTs performed every 3 months before and after therapy start. FVC% and DLCO% slope is calculated as change per month before and after treatment start. AZA: Azathioprine; MMF: Mycophenolate; IS: Immunosuppression

The mean FVC% before mycophenolate therapy was 55%, and the mean FVC% after therapy was 61% (p = 0.34). DLCO% slope was declining at a rate of -4% change per month before therapy and -1% after therapy (p = 0.01) (Figure 3B, Table 2). The mean DLCO% before therapy was 45% and after was 42% (p = 0.59).

Rituximab Group

Five out of six patients treated with rituximab had received or were receiving treatments with mycophenolate or azathioprine. Only three patients had PFTs available before and after treatment. Overall, an improvement in FVC% and decline inDLCO% after treatment with rituximab was noted. The FVC% change of slope before treatment was a rate of 9% per month and after treatment was 3% per month (p = 0.18). The DLCO% slope before therapy was 5% per month and after therapy was -2% per month (p = 0.43).

UIP vs. Composite Group

To determine if treatment response to immunosuppression varied between UIP and other ILD patterns, sensitivity analysis of UIP versus a composite group (LIP, NSIP, and OP) before and after treatment was performed. In the analysis of UIP versus other ILD patterns we found that FVC% slope improved an average of 9% per month for UIP and 3% for the composite group (p = 0.06). DLCO%

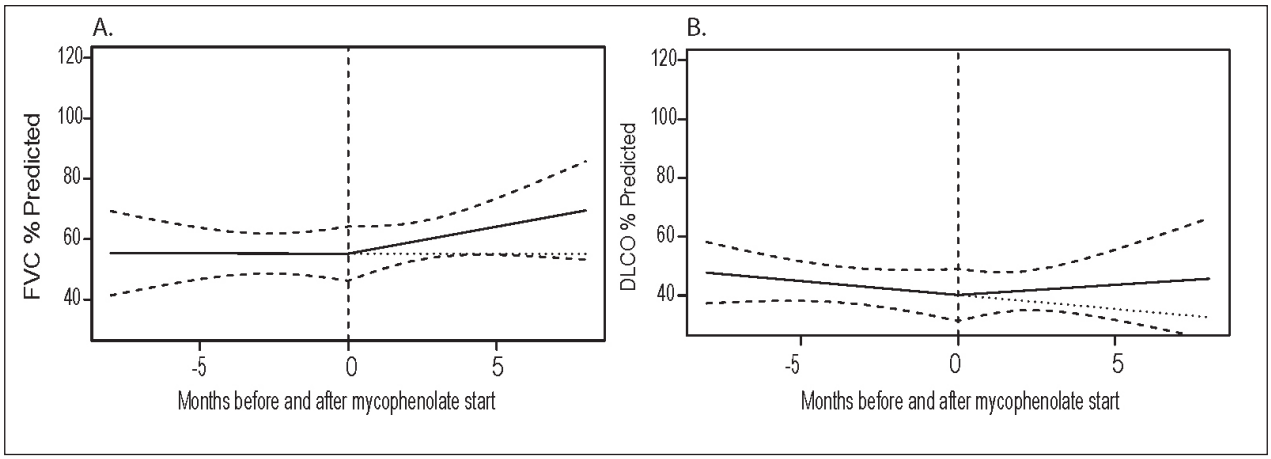

Fig. 3. Mixed-effects model estimate of FVC% and DLCO% slope before and after initiation of mycophenolate plotted 12 months before and 12 months after mycophenolate start. The bold perforated line represents the 95% confidence interval. The light perforated line represents the trajectory of the pre-treatment slope. (a) FVC% slope before treatment was declining at a rate of -9.8% per month and after treatment was increasing at a rate of 2.1% per month (p = 0.02); (b) DLCO% slope before treatment was declining at a rate of -3.8% per month and after treatment was declining at a rate of -1.3% per month (p = 0.01).

improved by a mean 1% per month in the UIP group and 1% in the composite group (p = 0.96).

Discussion

ILD is a common complication of pSS that significantly increases morbidity and mortality. Despite these implications for patient's well-being, the optimal management of pSS-ILD remains unknown. Because there is no well-defined or standard approach to therapy that is supported by clinical trial data, we sought to determine the real-world efficacy of commonly utilized immunosuppressive medications.

In this retrospective, observational cohort study we identified well-matched cohorts of patients with pSS-ILD who had received either azathioprine or mycophenolate as the primary steroid-sparing immunosuppressive agent. Analysis of pre- and post- treatment PFTs showed that initiation with azathioprine was associated with a trend toward improvement in PFT parameters. Fitting these findings using a mixed effects model, comparison of pre-treatment FVC% decline compared with post-treatment FVC% decline suggested a trend toward stabilization, although the study may have been underpowered to directly test this outcome. In the second cohort of patients treated with mycophenolate, we observed improved PFTs after initiation of therapy with the mixed effects model showing a similar stabilization in FVC% and DLCO% decline. Of clinical importance, prednisone use decreased significantly after start of mycophenolate therapy and a similar trend was noted with azathioprine therapy.

Chart review of both of these cohorts found that both azathioprine and mycophenolate were well-tolerated with most patients able to remain on therapy for an extended time (median 7.3 years for azathioprine and 1.9 years for mycophenolate). Taken together, these data support the use of mycophenolate as a treatment for pSS-ILD, and suggest that azathioprine may have a similar efficacy.

A further strength of this study is the granular examination of longitudinal PFT data, which enabled us to utilize a mixed effects model to estimate the magnitude of effect on PFT decline pre- and post-initiation of therapy. This model suggests that, in aggregate, mycophenolate completely attenuated the FVC% decline, which fits with the observed change in pre- and post-FVC% values. This finding adds to our understanding of the potential effect of mycophenolate on lung function decline for this subset of ILD, as other efficacious therapies for idiopathic ILDs such as IPF are known to decrease the FVC% decline, but do not fully stabilize disease in aggregate (14, 15). Too few subjects were available that had received only rituximab and who had

sufficient PFT data available before and after therapy initiation to adequately evaluate its potential efficacy.

These findings add to the limited existing published data studying the efficacy of mycophenolate in pSS-ILD. Mycophenolate has been studied as part of a large CTD-ILD cohort including pSS patients and reported to possibly improve lung function, but only four of a total of 67 patients with CTD-ILD had pSS (12). Thus, definitive conclusions about its efficacy in pSS-ILD could not be drawn. Our cohort significantly adds to our understanding of the effects of mycophenolate on pSS-ILD. Our work represents the largest reported well-characterized cohort of pSS-ILD patients treated with mycophenolate for lung function decline. Furthermore, along with the observed stable lung function post mycophenolate initiation, we identified a significant reduction in prednisone dosage, which is often an important aim of initiating this therapy in patients. In aggregate, these findings lend further support to the potential efficacy of mycophenolate in this patient population.

Similar to mycophenolate, this study adds to the limited existing published data studying the efficacy of azathioprine in pSS-ILD. In the largest published cohort of pSS-ILD patients treated with azathioprine, Deheinzelin et al. found that the FVC improved in seven of eleven patients (10). While other studies have reported potentially improved outcomes in patients with pSS-ILD on azathioprine, these studies grouped pSS patients into a larger CTD cohort, precluding analysis of individual disease types (11). Thus, in this report we describe the second largest cohort of patients with pSS-ILD treated with azathioprine. Although our study was likely underpowered to detect differences in pre- and post- FVC% changes, mixed effects modeling suggested that there is stabilization of FVC% decline after treatment initiation.

Although an analysis of the efficacy of rituximab was a goal of this study, we had limited data available on pre- and post-treatment PFTs in the rituximab group. Previous studies reporting rituximab efficacy have been small, ranging from one to eight pSS-ILD patients treated with rituximab (16-18). Our limited series of patients treated with rituximab had mixed PFT change after therapy. Of the three patients with pre- and post-PFT data, all were treated with another immunosuppressive agent prior to initiation of rituximab, confounding the interpretation of these data.

We performed sensitivity to evaluate pre and post FVC% and DLCO% when comparing UIP to composite ILD (LIP, NSIP, and OP). No significant difference was seen in treatment response between UIP and NSIP, supporting that histopathology pattern did not significantly influence our reported findings. Further, the distribution of UIP was similar between the three treatment cohorts. Interestingly, there was a trend toward greater improvement of FVC% in the UIP group compared to the composite group, although this did not reach significance. Previous series have suggested that pSS UIP prognosis is similar to that of NSIP, while others show pSS UIP is progressive and resistant to immunosuppressive therapy (3, 9).

Limitations of our study include its retrospective nature and the small number of patients who met inclusion criteria that allowed them to be placed in the treatment cohorts. The retrospective nature of this study may confer bias and limits our ability to draw conclusions concerning causal relationships of specific therapies with outcomes. Intrinsic to a retrospective study, there was variability between comparator groups. For example, the untreated group had an overall older age than the treated groups. Despite older age, the untreated group had a similar baseline functional capacity including baseline PFT values and oxygen requirement. Although baseline 6-minute walk tests varied between the four groups at baseline, interpretation of these results are limited by a paucity of data. Additionally, many patients were treated with other immunosuppressive therapy such as corticosteroids, however doses of corticosteroids were similar between the groups and declined after initiation of azathioprine and mycophenolate, making this less likely to have confounded our results. Two patients treated with immunosuppressive therapy were diagnosed by HRCT alone without pathology. In the case of HRCT-diagnosed NSIP, a histopathologic diagnosis of UIP might falsely reduce the significance of the results. Reassuringly, despite this limitation, we did find significant improvement in FVC% with mycophenolate therapy. One case of LIP treated with azathioprine was not biopsied. Biopsy of LIP is important because both pulmonary amyloidosis and lymphoma can appear similar to LIP. However, in this case the patient was followed

over 15 years for stable ILD, making the presence of occult amyloidosis or lymphoma unlikely. Also, because out center is a tertiary referral center, our pSS-ILD cohort may have referral bias toward more severe disease. Finally, improved PFT values may only reflect a survival effect that was not linked to a beneficial treatment response.

In conclusion, in this retrospective cohort analysis of well-characterized pSS-ILD patients treated with either azathioprine or mycophenolate we found that mycophenolate treatment was associated with a significant improvement in pulmonary function that appeared durable by mixed effects modeling. These findings significantly expand the limited available data supporting the use of azathioprine and mycophenolate as therapies for these patients. This study has found compelling associations between the use of azathioprine and mycophenolate in pSS-ILD and lung function stabilization. However, due to the retrospective and observational nature of this study, adequately powered prospective studies are still needed to further validate the potential efficacy of these immunomodulatory therapies on disease progression in pSS-ILD.

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A real-world study of the dosing and tolerability of pirfenidone and its effect on survival in idiopathic pulmonary fibrosis

Sahajal Dhooria[1], Ritesh Agarwal[1], Inderpaul Singh Sehgal[1], Kuruswamy Thurai Prasad[1], Valliappan Muth[1], Mandeep Garg[2], Amanjit Bal[3], Ashutosh Nath Aggarwal[1], Digambar Behera[1]

[1]Department of Pulmonary Medicine, [2]Department of Radiodiagnosis and Imaging, [3]Department of Histopathology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Abstract. *Background:* Patients with idiopathic pulmonary fibrosis (IPF) often do not tolerate pirfenidone in the recommended dose of 2400 mg/day. The proportion of patients requiring dose reduction and its impact on survival in the real-world remain unclear. *Methods:* Consecutive subjects with IPF were enrolled between March 2017 and June 2019. The maximum tolerated dose of pirfenidone (primary outcome) and adverse drug reactions (ADRs) were recorded. A post hoc logistic regression analysis was performed to evaluate the predictors of drug discontinuation due to ADRs. We also compared survival between the full-dose (2400 mg/day), reduced-dose (< 2400 mg/day), and the no-pirfenidone groups, with age and percentage of the predicted forced vital capacity (%pred FVC) as covariates. *Results:* Of the 128 subjects (mean age, 67.4 years; 77.3% men) included, 115 were initiated on pirfenidone. Forty-nine (42.6%) and 51 (44.3%) subjects tolerated the full dose and reduced doses, respectively. Ninety-six (83.5%) subjects developed at least one ADR; anorexia dyspepsia, and nausea being the most common. Twenty-two subjects discontinued the drug; 15 of them due to ADRs. Body mass index < 20 kg/m^2 was the only predictor of drug discontinuation due to ADRs. Among subjects newly initiated on treatment during the study period (n = 80), survival was longer (hazard ratio [interquartile range], 0.19 [0.04-0.96]; p = 0.045) in the full-dose but not the reduced-dose group (p = 0.08) compared with the no-pirfenidone group, after adjusting for covariates. *Conclusion:* Pirfenidone was tolerated in the full dose in a minority of patients with IPF and appears to improve survival only with the full dose. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 148-157)*

Key words: interstitial lung disease, interstitial pneumonia, diffuse lung disease, lung fibrosis, drug safety, antifibrotic

Received: 25 July 2019
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Correspondence: Dr. Sahajal Dhooria MD, DM
Assistant Professor
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh-160012, India
Phone: +91 172 275 6823
Fax: +91 172 274 8215
Email: sahajal@gmail.com

Introduction

Idiopathic pulmonary fibrosis (IPF) is a diffuse lung disease associated with a reduced survival.(1, 2) The disease advances inexorably with deteriorating lung function due to progressive lung fibrosis. The antifibrotic agents pirfenidone and nintedanib are the only drugs that benefit patients with IPF.(3, 4) Pirfenidone was found to reduce the rate of decline in the forced vital capacity (FVC) in two of the three phase 3 multinational, randomized trials (CAPACITY 1, CAPACITY 2, and ASCEND).(3, 5) In a pooled analysis of these studies, pirfenidone was also found to reduce the risk of death at one year.(3) The dose of pirfenidone associated with a survival advantage was 2403 mg/day.

Several studies have reported the use of pirfenidone in IPF in clinical practice.(6-11) These studies indicate that the full dose of pirfenidone is poorly tolerated in a large number of patients and frequently requires dose reduction.(9) The discontinuation rates are also high in the real-world like that in the clinical trial setting.(3, 6, 9) The effect of pirfenidone on survival is inconsistent among real-world studies.(12-17) One reason for this inconsistency could be the varying doses of pirfenidone that patients tolerate in clinical practice. In an analysis of the pooled data from the CAPACITY and ASCEND trials, as compared to placebo, pirfenidone did not change the outcome of progression or death at one year when used in reduced doses.(18) Unfortunately, there is a dearth of prospective real-world data on the effect of reduced doses of pirfenidone on survival in IPF.

Herein, we describe our experience with the dosing and tolerability of pirfenidone in patients with IPF. We analyze the factors associated with the discontinuation of pirfenidone due to adverse drug reactions (ADRs). We also compare the survival of subjects receiving the full dose or reduced doses of the drug.

Material and Methods

This prospective, observational study was performed between March 2017 and June 2019 at the Chest Clinic of this Institute. The Institutional Ethics Committee approved the study protocol, and all subjects provided a written informed consent.

Study subjects

We included consecutive subjects presenting to the Chest Clinic if they (1) were diagnosed to have IPF; and, (2) consented to participate in the study. Subjects newly diagnosed during the study period formed the prospective cohort. We also included patients diagnosed before the study period and already following up in the clinic (whether or not taking pirfenidone), whom we designated as the retrospective cohort. The following subjects were excluded: (1) subjects who opted for nintedanib; and, (2) subjects who refused consent for the study. A diagnosis of IPF was made based on the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association criteria, as described previously.(1, 19) A lung biopsy (either a surgical lung biopsy [SLB] or a transbronchial lung cryobiopsy [TBLC]) was considered, wherever the clinician, in consultation with the radiologist, considered the diagnosis of IPF to be in doubt after reviewing the clinical and radiologic data. The biopsy was performed if the subject was willing and fit for the procedure. The degree of confidence in the diagnosis (confident, or provisional with high or low confidence) was assigned in each case by the multidisciplinary discussion (MDD) team, according to a proposed classification.(20)

Study procedure

We recorded the demographic details and comorbid illnesses of the included subjects, the spirometric findings (FVC, percentage of the predicted FVC [% predicted FVC], forced expiratory volume in one second [FEV_1], % predicted FEV_1, FEV_1/FVC ratio, and the type of spirometric abnormality), diffusion capacity of the lung for carbon monoxide (DLCO), resting oxygen saturation, and the six-minute walk distance. Subjects were started on pirfenidone, after being explained the risks and benefits of the medication.(2) We initiated pirfenidone at a dose of 600 mg/day in three divided doses and gradually escalated the daily dose to 2400 mg. The ADRs were recorded. In the case of intolerable ADRs, titration to the maximum tolerated dose was performed. If a subject did not tolerate a minimum dose of 600 mg/day, the drug was stopped.(21) We offered the option of switching to nintedanib to subjects who

discontinued pirfenidone due to ADRs, did not tolerate the full-dose, or had disease progression on pirfenidone. We followed the subjects longitudinally during the study period at planned intervals of six months between visits. An acute exacerbation of IPF (AE-IPF) was defined as an acute (over < 1 month) worsening of respiratory symptoms and/or lung function in the absence of an alternate diagnosis (such as respiratory tract infection, aspiration, drug toxicity, heart failure, pulmonary embolism, and other such conditions).(22) We recorded the outcomes of all study subjects. For the survival analysis, we first divided the study population into two groups: pirfenidone group (those who were started on pirfenidone and continued the drug until death or last follow up) and the no-pirfenidone group (those who did not receive pirfenidone or discontinued it within six months). For the second analysis, the pirfenidone group was divided into the full-dose group (those receiving a stable dose of 2400 mg/day of pirfenidone) and reduced-dose group (those receiving less than 2400 mg/day), and was compared with the third group (the no-pirfenidone group).

Study Outcomes

The primary outcome of the study was to identify the actual tolerated doses of pirfenidone in subjects with IPF in a real-world situation. The secondary outcomes included the assessment of the adverse effects of pirfenidone and the efficacy of the drug (lung function decline). Post hoc exploratory analyses of the predictors of discontinuation of pirfenidone due to ADRs and of survival in the different pirfenidone dosing groups were performed.

Statistical analysis

Data were analyzed using the statistical package SPSS (version 23.0, IBM Inc., Armonk, NY, United States). Statistical significance was assumed at a p-value < 0.05. A sample size calculation was not performed at study initiation as the study was planned as an observational study. The data are expressed as number with percentage, mean with standard deviation, or median with interquartile range (IQR), as appropriate. The differences between categorical variables were analyzed using the chi-square test (or the Fisher's exact test) while the differences between continuous variables were analyzed using the one-way analysis of variance or the Kruskal-Wallis test. The annualized decline in % predicted FVC was calculated by dividing the decrease in the absolute value of % predicted FVC by the interval (in years) between the measurements. A missing-value analysis was not performed. A logistic regression analysis was performed to identify the predictors for the discontinuation of pirfenidone due to ADRs. A multivariate Cox regression analysis was performed to study the factors associated with survival in the study groups in the prospective cohort. Age, % predicted FVC (at the start of the maximum tolerated dose), and the study group were entered as covariates. Percentage predicted FVC was assumed as 25% as a worst-case scenario (only for the survival analysis), for subjects who could not perform an acceptable spirometric maneuver at the initiation of the maximum tolerated dose. The hazard ratio (HR) with 95% confidence intervals (CI) were calculated. We also performed secondary analyses for survival for the entire cohort and a survival analysis with additional covariates for the prospective cohort.

Results

Of the 139 subjects screened, 128 (mean age, 67.4 years; 77.3% men) were enrolled (Table 1). Nine refused consent, while two opted for nintedanib. The definite, probable, and indeterminate patterns for UIP were present in 93 (72.7%), 26 (20.3%), and 9 (7.0%) subjects, respectively on the HRCT of the chest. A confident diagnosis on MDD was made in 108 (84.4%) subjects, while 20 received a provisional diagnosis (16 [12.5%] with high confidence, and 4 [3.1%] with low confidence). Only four subjects underwent a lung biopsy (three TBLC, one SLB). Among the nine subjects with an indeterminate pattern on HRCT, two underwent TBLC and received a confident and provisional (with high confidence) MDD diagnosis, respectively. In the remaining seven subjects (median age, 74 years), a provisional 'clinical best-fit diagnosis' of IPF (three high confidence and four low confidence) was made by the MDD team in view of age, clinical presentation, and the absence of any history of connective tissue disorders, and exposure to offending drugs or environmental dusts. Four subjects were lost to follow up. Of the included subjects, 80 constituted the prospective

Table 1. Baseline characteristics of study subjects (n = 128)

Parameter	Value
Age, years	67.4 ± 7.8
Men, Number (%)	99 (77.3)
Body mass index, kg/m^2	24.2 ± 4.5
Any smoke exposure	71 (55.5)
Tobacco smoking	59 (46.1)
Biomass smoke exposure	13 (10.2)
Comorbid illnesses	
Hypertension	45 (35.2)
Diabetes mellitus	25 (19.5)
Coronary artery disease	17 (13.3)
Chronic obstructive pulmonary disease	8 (6.3)
Hypothyroidism	7 (5.5)
Chronic liver disease	3 (2.3)
Cerebrovascular disease	1 (0.8)
Gastroesophageal reflux	43 (33.6)
Duration of symptoms, months	10.5 (6-24)
Oxygen saturation, %	95 (92-97)
Spirometric abnormality (n = 115)	
Obstructive defect	8 (6.3)
Restrictive defect	80 (62.5)
Normal	27 (21.1)
Could not perform	13 (10.2)
Spirometric parameters (n = 115)	
FVC, litres	2.14 ± 0.65
FVC, % predicted	70.0 ± 17.5
FEV1, litres	1.75 ± 0.49
FEV1, % predicted	74.6 ± 17.8
DLCO, % predicted (n = 81)	48.8 ± 19.3
Six-minute walk distance, meters (n = 103)	372 ± 79
Presence of emphysema on HRCT chest	25 (19.5)
Presence of pulmonary hypertension	29 (22.7)
Use of domiciliary oxygen during the clinical course	29 (22.7)

All values represent mean ± standard deviation, median (interquartile range), or number (percentage). DLCO-diffusion capacity of the lung for carbon monoxide, FEV1-forced expiratory volume in one second, FVC-forced vital capacity, HRCT-high resolution computed tomography

cohort, with a median (IQR) duration of follow up of 15 (6-20) months. There were 48 subjects in the retrospective cohort with a median (IQR) follow up of 40 (25-53) months from their initial clinic visit.

Table 2. Tolerated dose/dose range of pirfenidone (primary outcome) and reasons for discontinuation among study subjects started on pirfenidone (n = 115)

Tolerated dose/dose range	Number (percentage)
2400 mg	49 (42.6)
1800 mg to < 2400 mg	34 (29.6)
1200 mg to < 1800 mg	12 (10.4)
600 mg to < 1200 mg	5 (4.3)
Reasons for discontinuation (n = 22)	**Number (percentage)**
Discontinued due to an adverse drug reaction	15 (68.2)
Patient's choice	4 (18.2)
Progression prompting a switch to nintedanib	2 (9.1)
Financial constraint	1 (4.5)

They had been receiving pirfenidone for a median (IQR) duration of 18 (11-34) months before enrolment into the study.

Pirfenidone was initiated in 115 (89.8%) subjects; the reasons for not starting the drug in the remaining were patient's choice (n = 7), advanced disease (n = 3), financial constraints (n = 2), and decompensated cirrhosis (n = 1), respectively. Forty-nine (42.6%) subjects tolerated the full dose and 51 (44.3%) tolerated a reduced-dose (primary outcome; Table 2). The drug was discontinued in 22 (19.1%) subjects; in 12, it was within six months of initiation. Among the 22 subjects who discontinued the drug, 15 were due to ADRs, four due to patient's choice, two had progression and were switched over to nintedanib; one subject discontinued due to financial constraint. Table 3 depicts the ADRs due to the drug; 96 (83.5%) subjects experienced at least one ADR. In the univariate and multivariate logistic regression analyses, body mass index (BMI) < 20 kg/m^2 was the only factor that predicted drug discontinuation due to ADRs, amongst other factors including age, gender, % predicted FVC, presence of any comorbidity, and presence of gastroesophageal reflux (Table 4).

The median (IQR) annualized fall in % predicted FVC was not significantly different (p = 0.32) between the full-dose (4.5 [-1.3, 8.7]) and reduced-dose (5.5 [3.0, 10.1]) groups (secondary outcome). Twenty-nine (22.7%) subjects had at least one AE-IPF; 11 (22.0%), 13 (24.5%) and 5 (20.0%) subjects in the full-dose, reduced-dose, and no-pirfenidone groups, respectively. The occurrence of AE-IPF was

Table 3. Adverse drug reactions on pirfenidone treatment (n = 115)

Adverse drug reaction	Number (percentage)
Any adverse drug reaction	96 (83.5)
Anorexia	48 (41.7)
Dyspepsia	34 (29.6)
Nausea	22 (19.1)
Uneasiness	20 (17.4)
Rash	20 (17.4)
Weight loss	17 (14.8)
Itching	16 (13.9)
Insomnia	16 (13.9)
Giddiness	13 (11.3)
Flushing	9 (7.8)
Raised liver transaminases	8 (7.0)
Vomiting	8 (7.0)
Dry mouth	7 (6.1)
Others*	25 (21.7)

*Other adverse drug reactions each with a frequency of < 5% included abdominal pain, chest congestion, constipation, diarrhea, drowsiness, fatigue, forgetfulness, headache, hoarseness of voice, increased cough, irritability, mucositis, nasopharyngitis, numbness, paraesthesia, slurred speech, somnolence, and vertigo.

not significantly different between the study groups (p = 0.89). Overall, 40 (31.3%) subjects died during the study period; 23 in the prospective cohort. A comparison of baseline characteristics of the subjects in the full-dose, reduced-dose, and the no-pirfenidone groups in the prospective cohort is provided in Supplementary Table 1. In the prospective cohort, subjects in the pirfenidone group survived longer (HR [IQR], 0.33 [0.12-0.88]; p = 0.03) than in the no-pirfenidone group (Table 5; Figure 1A). When analyzed separately for the full-dose and reduced-dose groups, the hazards for death were reduced (HR [IQR], 0.19 [0.04-0.96]; p = 0.045) only with the use of the full dose (Table 5; Figure 1B). With the use of additional covariates, the % predicted FVC and the number of comorbidities were also found to be associated with lower hazards for death apart from the use of full-dose pirfenidone (Supplementary Table 2). When analyzed for the entire population (prospective and retrospective cohorts), the survival was significantly improved in both the full-dose and reduced-dose groups compared to the no-pirfenidone group (Table 5).

Table 4. Univariate and multivariate logistic regression analyses of factors predicting discontinuation of pirfenidone due to adverse drug reactions

	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.03 (0.96-1.10)	0.46	1.05 (0.97-1.14)	0.23
Female gender	0.84 (0.22-3.22)	0.79	0.53 (0.10-2.76)	0.45
Body mass index < 20 kg/m^2	4.05 (1.17-14.02)	**0.03**	5.29 (1.22-23.06)	**0.03**
% predicted FVC	1.00 (0.97-1.04)	0.83	1.01 (0.98-1.04)	0.63
Any comorbidity*	1.33 (0.44-1.02)	0.61	1.63 (0.45-5.87)	0.46
Gastroesophageal reflux	1.86 (0.62-5.57)	0.27	1.82 (0.51-6.47)	0.35

*The comorbidities considered were as listed in Table 1. CI-confidence intervals, FVC-forced vital capacity, OR-odds ratio

Supplementary Table 1. Comparison of baseline characteristics between subjects in different pirfenidone groups in the prospective cohort (n = 80)

Parameter	Full-dose group (n = 24)	Reduced-dose group (n = 35)	No-pirfenidone group (n = 21)	p-value
Age, years	65.5 ± 7.9	67.9 ± 8.5	70.4 ± 7.3	0.13
Men, Number (%)	20 (83.3)	24 (68.6)	17 (81.0)	0.36
Body mass index, kg/m^2	24.4 ± 5.2	24.3 ± 4.1	23.7 ± 6.1	0.89
Any smoke exposure	16 (66.7)	20 (57.1)	12 (57.1)	0.73

Parameter	Full-dose group (n = 24)	Reduced-dose group (n = 35)	No-pirfenidone group (n = 21)	p-value
Tobacco smoking	15 (62.5)	16 (45.7)	10 (47.6)	0.42
Biomass smoke exposure	1 (4.2)	5 (14.3)	2 (9.5)	0.44
Comorbid illnesses				
Any comorbidity	13 (54.2)	23 (65.7)	14 (66.7)	0.60
Hypertension	5 (20.8)	15 (42.9)	12 (57.1)	**0.04**
Diabetes mellitus	8 (33.3)	6 (17.1)	3 (14.3)	0.22
Coronary artery disease	3 (12.5)	5 (14.3)	3 (14.3)	0.98
Chronic obstructive pulmonary disease	2 (8.3)	3 (8.6)	1 (4.8)	0.86
Hypothyroidism	4 (16.7)	0	0	**0.007**
Chronic liver disease	1 (4.2)	1 (2.9)	1 (4.8)	0.93
Cerebrovascular disease	0	0	0	0.46
Gastroesophageal reflux	13 (54.2)	12 (34.3)	9 (42.9)	0.32
Duration of symptoms, months	12 (5-23)	10 (6-24)	10 (6-30)	0.93
Pattern on HRCT chest				
Definite UIP	18 (75.0)	24 (68.6)	19 (90.5)	0.35
Probable UIP	4 (16.7)	6 (17.1)	2 (9.5)	
Indeterminate for UIP	2 (8.3)	5 (14.3)	0	
Presence of emphysema on HRCT chest	8 (33.3)	7 (10.0)	6 (28.6)	0.50
Presence of pulmonary hypertension	5 (20.8)	7 (20.0)	3 (14.3)	0.83
Level of confidence of MDD diagnosis				
Confident	20 (83.3)	25 (71.4)	19 (90.5)	0.25
Provisional with high confidence	4 (16.7)	7 (20.0)	2 (9.5)	
Provisional with low confidence	0	3 (8.6)	0	
Use of domiciliary oxygen	4 (16.7)	8 (22.9)	5 (23.8)	0.80
Baseline oxygen saturation, %	95 (92-97)	95 (93-97)	94 (91-97)	0.69
Spirometric parameters	(n = 21)	(n = 31)	(n = 16)	
Type of spirometric abnormality				
Obstructive defect	2 (9.5)	3 (9.7)	1 (6.3)	0.93
Restrictive defect	16 (76.2)	23 (74.2)	11 (68.8)	
Normal	3 (14.3)	5 (16.2)	4 (25.0)	
FVC, litres	1.96 ± 0.44	1.99 ± 0.61	2.04 ± 0.64	0.92
FVC, % predicted	70.6 ± 19.2	71.7 ± 16.9	72.6 ± 16.2	0.67
FEV1, litres	1.69 ± 0.36	1.63 ± 0.49	1.67 ± 0.49	0.91
FEV1, % predicted	70.6 ± 19.2	71.7 ± 16.9	72.6 ± 16.2	0.94
DLCO	(n = 19)	(n = 18)	(n = 10)	
% predicted	48.7 ± 21.7	46.2 ± 18.4	58.3 ± 23.5	0.34
Six-minute walk test	(n = 21)	(n = 30)	(n = 12)	
Distance, meters	360 ± 85	345 ± 52	377 ± 80	0.39

All values represent mean ± standard deviation, median (interquartile range), or number (percentage). DLCO-diffusion capacity of the lung for carbon monoxide, FEV1-forced expiratory volume in one second, FVC-forced vital capacity, HRCT-high resolution computed tomography

Table 5. Cox regression for survival among study subjects

Covariates	HR (95% CI)	p-value
Prospective cohort (n = 80)		
Pirfenidone group	0.33 (0.12-0.88)	**0.03**
Age	1.02 (0.96-1.08)	0.55
% predicted FVC at start of dose	0.98 (0.95-1.00)	0.05
Prospective cohort (n = 80)		
Full-dose group	0.19 (0.04-0.96)	0.045
Reduced-dose group	0.40 (0.14-1.12)	0.08
Age	1.01 (0.95-1.08)	0.74
% predicted FVC at start of dose	0.98 (0.95-1.00)	0.06
Entire cohort (n = 126)*		
Pirfenidone group	0.31 (0.13-0.70)	**0.01**
Age	1.01 (0.96-1.05)	0.79
% predicted FVC at start of dose	0.97 (0.95-0.99)	< **0.001**
Entire cohort (n = 126)*		
Full-dose group	0.29 (0.12-0.74)	**0.01**
Reduced-dose group	0.32 (0.13-0.78)	**0.01**
Age	1.01 (0.96-1.05)	0.81
% predicted FVC at start of dose	0.97 (0.95-0.99)	< **0.001**

*Two subjects, who switched to nintedanib were excluded from the analysis. CI-confidence intervals, FVC-forced vital capacity, HR-hazard ratio

Discussion

The results of this study suggest that a large proportion of our patients with IPF did not tolerate the full dose of pirfenidone. Pirfenidone improved survival, compared to those who did not receive the drug, only when used in the maximum approved dose of 2400 mg/day. A lower BMI (< 20 kg/m2) was associated with discontinuation of the drug due to ADRs.

We found that only about 42% of the study subjects tolerated the full dose of pirfenidone like in previous studies, wherein 41-45% subjects required dose reduction.(9, 23) In fact, in real-world studies from Japan, the usual targeted and tolerated dose was only 1800 mg.(6, 24) In contrast, in studies from Italy, Germany and the United States, 83-89% of the patients were compliant with a dose of 2403 mg/day. (7, 8, 10) Thus, ethnicity and body weight (with Europeans generally having a higher body weight than Asians) might be potential factors affecting the tolerated dose. The most common ADRs in our study were anorexia, dyspepsia and nausea, again mimicking the observations in previous real-world studies.(9, 25) A significant proportion of our subjects also complained of a feeling of marked 'uneasiness'

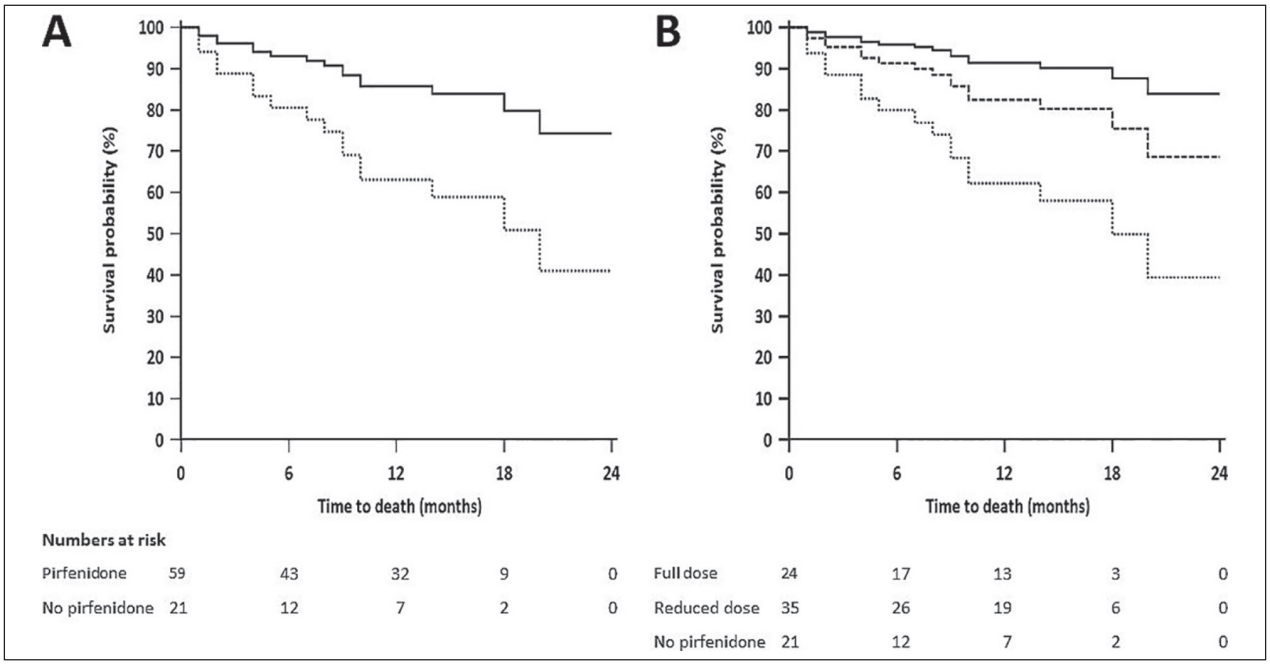

Fig. 1. Cox regression analysis for survival in the prospective cohort. **A**. Two-group analysis (pirfenidone vs. no-pirfenidone); **B**. Three group analysis (full-dose pirfenidone, and reduced-dose pirfenidone vs. no-pirfenidone). The covariates were age, and % predicted forced vital capacity.

encountered due to the drug, which could not be characterized any further.

We found that the hazards for death were significantly reduced with the use of pirfenidone in the real-world, similar to the results of the phase 3 trials.(3, 5) Other real-world studies have been more equivocal about the survival advantage with pirfenidone use in IPF (Table 6).(12-17) In the Czech EMPIRE registry, pirfenidone increased the overall survival of patients with IPF at five years over no-antifibrotic treatment.(17) In the Spanish SEPAR registry, however, the median survival of subjects receiving pirfenidone was similar to the entire cohort. (14) While Margaritopoulos et al. found improved survival with pirfenidone compared to a retrospective cohort, in the Finnish IPF registry analysis, the survival advantage with pirfenidone disappeared after adjustment for age.(13, 16) In our study, the hazards for death were lower, even after adjusting for age and % predicted FVC. Importantly, when analyzed separately for the full-dose and reduced-dose groups, we found improved survival only in the full-dose group. These findings are similar to a post hoc analysis of the pooled data from the CAPACITY and ASCEND trials.(18) In that study, the outcome of progression or death at one year was decreased for subjects who received the full dose of pirfenidone vs. placebo, but not so, with a reduced dose intensity (≤ 90% of the full dose). Moreover, in an earlier phase 3 trial from Japan, Taniguchi et al. also found a significantly better survival (p = 0.03) with a higher dose (1800 mg/day) of pirfenidone compared to a lower dose

Supplementary Table 2. Cox regression for survival among the prospective cohort (n = 80) of study subjects with the inclusion of additional covariates

Covariates	HR (95% CI)	p-value
Full-dose group	0.16 (0.03-0.85)	**0.03**
Reduced-dose group	0.41 (0.14-1.21)	0.11
Age	1.01 (0.94-1.07)	0.87
Male Gender	1.76 (0.37-8.31)	0.47
Smoke exposure	0.92 (0.33-2.58)	0.88
Number of comorbidities	0.45 (0.21-0.95)	**0.04**
Presence of pulmonary hypertension	0.37 (0.07-1.88)	0.23
% predicted FVC at start of dose	0.97 (0.94-0.99)	**0.03**

Table 6. Real-world studies of survival with the use of pirfenidone in subjects with IPF

Authors (Year)	Number	Number treated with pirfenidone	Dose of pirfenidone used	Comparator	Findings
Natarajan, et al. (2015)(12)	46	17	1200-1800 mg/day	Triple therapy	No significant difference in survival
Margaritopoulos, et al. (2018)(13)	294	82	2403 mg/day	Historical cohort not receiving pirfenidone	Survival improved with pirfenidone; HR: 0.32 (95% CI, 0.19–0.53; p < 0.0001)
Fernández-Fabrellas, et al. (2019)(14)	608	231	NA	Entire cohort	Median survival of subjects receiving pirfenidone similar to the entire cohort (5.8 years)
Jouneau, et al. (2019) (15)	192	192	2403 mg/day (32.3% subjects had a dose reduction)	None	Median progression-free survival: 18.4 months
Kaunisto, et al. (2019)(16)	453	82 (13 received nintedanib)	NA	Subjects not receiving any antifibrotic	Survival not different; HR: 0.67 (95% CI, 0.43–1.05; p = 0.078)
Zurkova, et al. (2019)(17)	841	383	2403 mg/day (dose reduction NA)	Subjects not receiving any antifibrotic	Pirfenidone increased five year overall survival over no-antifibrotic treatment (55.9% vs 31.5% alive, p = 0.002)
Current study	128	100	Full-dose group: 2400 mg/day Reduced-dose group: < 2400 mg/day	Subjects not receiving any antifibrotic	Full-dose group HR: 0.19 (95% CI, 0.04-0.96; p = 0.045) Reduced-dose group HR: 0.40 (95% CI, 0.14-1.12; p = 0.08)

CI-confidence intervals, HR-hazard ratio, NA-not available

(1200 mg/day).(26) None of the previous real-world studies have separately analyzed the survival of subjects receiving full-dose or reduced-dose pirfenidone.

In contrast to the findings in the prospective cohort alone, in the entire population (comprising of both the prospective and retrospective cohorts), the subjects in both the full-dose and the reduced-dose groups had better survival than the no-pirfenidone group (Table 5). One explanation for this phenomenon may be the longer duration of follow up in the full cohort compared to the prospective cohort alone. It is possible that the survival advantage is similar with a reduced dose of pirfenidone to that with a full dose, when used over a longer-term. However, a more likely explanation is the attrition bias. Retrospective cohorts are susceptible to include subjects having a favorable response to the therapy of interest. Thus, patients with a good response to pirfenidone are more likely to remain under follow up compared to those who deteriorate.

We also performed a Cox proportional hazards analysis in the prospective cohort using additional covariates (pirfenidone dose group, age, male gender, smoke exposure, number of comorbidities, presence of pulmonary hypertension, and % predicted FVC at initiation of dose) (Supplementary Table 2). The essential finding of a survival advantage in the full-dose pirfenidone group remained unchanged. Additionally, we found that a higher % predicted FVC was associated with significantly lower hazards for death. Interestingly, a higher number of comorbidities was associated with reduced hazards for death. This counterintuitive finding is likely due to chance and also because adjusting for the 'number' of comorbidities does not permit an adjustment for the severity of such comorbidities.

We found that BMI < 20 kg/m2 was a significant predictor of drug discontinuation due to ADRs in a multivariate logistic regression analysis. Age was not a predictive factor in our study, in contrast to the findings of Galli, et al. who found age ≥70 years old to be a predictor apart from a history of congestive heart failure. (10) Our findings are, however, in conformity with the study by Uehara, et al., who found that subjects who received a higher dose of pirfenidone per kilogram of body weight had a higher incidence of adverse events.(27) Interestingly, a BMI < 22 kg/m^2 has also been found to be associated with a higher incidence of hepatotoxicity with the use of nintedanib in IPF.(28)

What are the clinical implications of our study? It is not uncommon for physicians to prescribe lower doses of pirfenidone in clinical practice.(29, 30) As pirfenidone offers survival advantage mainly with the full dose, it is imperative that an attempt be made to achieve this dose by slow dose escalation. In case, a patient is unable to tolerate the full dose, the option of switching to nintedanib may be discussed. In case, a patient does not opt for or tolerate nintedanib, one can still administer a lower dose of pirfenidone as the survival in the reduced-dose group also showed a trend towards improvement in our study (though statistically non-significant). Importantly, titration to the maximum tolerated dose should be performed, even in this scenario.

Our study has a few limitations. It is a single-center study with a small sample size and a relatively short duration of follow up. Therefore, the findings of the regression analysis should be interpreted cautiously. We did not plan an imputation analysis due to a large number of randomly missing values. This is because, in the real-world, patients present for follow up at variable intervals. Further, several of our subjects with advanced disease were unable to perform an acceptable spirometric maneuver. The survival analysis was a post hoc exploratory analysis in a cohort with varying follow-up durations and thus may suffer from an inadvertent immortal time bias. It is also possible that the small group of study subjects who did not receive pirfenidone showed a worse survival independent of the lack of treatment but rather due to a selection bias. Thus, this study offers only a preliminary insight into the effects of dose reduction of pirfenidone on survival in IPF, especially from the developing world. Larger, prospective, and preferably multicenter real-world studies, with longer duration of follow up, are required to confirm our findings. Studies of dosing are also needed for other potential indications of using pirfenidone, such as other fibrosing interstitial lung diseases.(31, 32)

In conclusion, the results of this study suggest that in actual clinical practice, pirfenidone is not tolerated in the full recommended dose of 2400 mg/day in a large proportion of patients. However, it appears that it offers a significant survival advantage, only when used in the full dose.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (1); 158-168 DOI: 10.36141/svdld.v37i1.9234

Predictors of cough-specific and generic quality of life in sarcoidosis patients

Branislav S. Gvozdenovic[1], Violeta V. Mihailovic-Vucinic[2,3], Mira H. Vukovic[4], Mihailo I. Stjepanovic[2,3], Ivana Buha[2], Strahinja V. Mihailovic[5], Nikola B. Maric[2]

[1] PPD Serbia, Pharmacovigilance Department, Belgrade, Serbia; [2] Clinic for Pulmonology, Clinical Centre of Serbia, Belgrade, Serbia; [3] Faculty of Medicine, University of Belgrade, Serbia; [4] QA Department, Health Centre Valjevo, Valjevo, Serbia; [5] Syneos Health, Belgrade, Serbia

Abstract. *Background:* Cough is frequent symptom in sarcoidosis and its impact on patient's quality of life (QoL) has not been adequately addressed so far. *Objectives:* The goal of this study was to determine the significant predictors of cough-specific and generic QoL in sarcoidosis patients. *Methods:* In the prospective study 275 sarcoidosis patients administered Patient Reported Outcomes instruments for measurement of dyspnea (Borg and MRC scales) and fatigue (Fatigue Assessment Scale (FAS) and Daily Activity List (DAL)), as well as patients' QoL (cough-specific Leicester Cough Questionnaire (LCQ) and generic tool – 15D). The LCQ contains 3 domains covering physical, psychological and social aspects of chronic cough. Pulmonary function tests (spirometry and diffusing capacity for carbon monoxide) and serum angiotensin converting enzyme (sACE) were also measured. *Results:* Dyspnea measured by Borg scale and impairment of daily activities determined by DAL instrument as well as sACE were the strongest predictors of all cough-specific QoL domains. Mental aspect of patients' fatigue was significantly correlated with all domains except with psychological LCQ domain. Regarding the generic QoL, the following significant predictors were: dyspnea measured by MRC scale, overall fatigue determined by FAS and physical domain of the LCQ. *Conclusion:* It is important to measure both cough-specific and generic QoL in sarcoidosis patients since they measure different health aspects and their predictors can be different. We demonstrated that physical domain of cough-specific QoL is significant predictor of generic QoL. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 158-168)*

Key words: Sarcoidosis, Quality of life, Cough, Dyspnea, Fatigue, sACE

Introduction

Sarcoidosis is a chronic multisystem granulomatous disease of unknown origin that most commonly affects the lungs but may also involve any other organ [1].

Patients with pulmonary sarcoidosis may have symptoms related directly to the chest such as dyspnea, chest pain and discomfort, cough, and wheeze. Patients may also develop symptoms related to extrapulmonary organ involvement. In addition, sarcoidosis may cause constitutional symptoms such as fatigue, fever, anorexia, weight loss, generalized weakness, and pain that are not related to involvement of any specific organ [2, 3]. Both organ-related and nonspecific sarcoidosis symptoms may significantly adversely influence patients' qulity of life (QoL).

Nowadays many tools for measurement of Patient-Reported Outcomes (PROs) as study endpoints have been developed in sarcoidosis [4]. PROs

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Correspondence: Branislav S. Gvozdenovic, MD, PhD
Specialist in Internal Medicine, Pulmonologist
55/15 Kralja Milutina Street, 11000 Belgrade, Serbia
Email: bgvozden@verat.net
Phone: +381 11 381 8603; Fax: +381 11 381 8601
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measure different aspects of a patient's health status that comes directly from the patient, without interpretation of the patient's responses by a physician or anyone else [5]. PROs encompass symptoms and signs of disease, treatment satisfaction and QoL of patients. This is increasingly observed as the regulatory authorities' requirement due to several limitations of the objective disease outcomes, like pulmonary function tests or radiographic findings.

Numerous studies showed that correlations between PROs as subjective outcomes and objective outcomes are rather mild or moderate or even do not exist at all [6]. QoL and 'functionality' are two most highly-rated outcomes for treatment and care by sarcoidosis patients [7,8]. The outcomes that are most important to patients should be considered to make sure that the recommendations in the international guidelines take into account aspects of treatment which matter to patients. They should participate in treatment decision making. For example, physician might prescribe steroids to improve patient's cough. The patient may choose not to take the steroids because the side effects (possible nausea, sleep problems, mood swings etc.) are worse for them than the cough. In that situation, the patients might rate what is more important for them.

Recently, more attention has been paid to the cough in patients with sarcoidosis. The mechanism of cough is unknown but airway inflammation, mechanical distortion from pulmonary fibrosis and disruption of the vagus nerve from mediastinal lymphadenopathy are possible [9]. However, the influence of cough on sarcoidosis patients' QoL has not been adequately addressed so far. There is a validated tool – Leicester Cough Questionnaire (LCQ) for measuring this important symptom [10]. The literature on LCQ use in sarcoidosis is limited – currently only a few studies used LCQ for assessing cough in sarcoidosis patients [11-13].

The aim of this study was to assess the significant predictors of both cough-specific and generic Qol in patients with pulmonary sarcoidosis.

Methods

In this prospective observational study in the period from April to December 2018 we enrolled 275 biopsy positive patients with pulmonary sarcoidosis diagnosed at the Clinic for Pulmonary Diseases of the Clinical Centre of Serbia in Belgrade, Serbia. All subjects were ≥ 18 years old and they did not have any associated ilnesses that could influence their health status (those with significant comorbidity, like cardiac or respiratory disorders other than sarcoidosis, were excluded). These patients were examined during regular clinical visits and the patients voluntarily completed the self-administered PROs, provided lab samples for sACE and performed pulmonary function testing. This study was approved by the institution's ethics committee and all patients consented to participation.

Following PROs were administered: 1) dyspnea instruments: Modified Medical Research Council (MRC) Dyspnea Scale [14] and Borg dyspnea category-ratio-10 scale (CR-10) [15], 2) fatigue questionnaires: Fatigue Assessment Scale (FAS) [16] and Daily Activity List (DAL) [17], and 3) QoL scales: Leicester Cough Questionnaire (LCQ) [10] and generic quality of life questionnaire 15D [18].

Modified Medical Research Council (MRC) Dyspnea Scale classifies subjects into one of five categories according to their degree of dyspnea when performing certain activities [14]. Scores range from the 0 to 4, with the higher scores indicating more severe dyspnea. We previously used it in patients with sarcoidosis [19,20].

Borg dyspnea category-ratio-10 scale (CR-10) [15] is an 11-point scale on which dyspnea is graded from 0 (nothing at all) to 10 (maximum). It is widely used in clinical practice and trials in different respiratory and cardiovascular diseases.

The Fatigue Assessment Scale (FAS) is a 10-item self-report fatigue questionnaire. Its five items represent physical and other five items indicate mental fatigue domains. The response scale is a 5-point Likert scale (1 never to 5 always). Total scores on the FAS can range from 10 to 50, with high scores indicating more fatigue. FAS total score < 22 indicates no fatigue. The psychometric properties (reliability and validity) of the FAS are good, and it was also shown in sarcoidosis patients [21,22,23]. The Serbian version proved to be valid in rheumatoid arthritis [24] and sarcoidosis [25].

The degree of limitation in daily life activities was evaluated with the Daily Activity List (DAL), a scale that was originally designed by Stewart and coworkers [17]. It has 11 items that are related to the usual activities that persons with good health

can perform without particular effort. The number of positive responses comprises the DAL score and indicates the degree of impairment. The scale has been used in several studies in patients with chronic pulmonary diseases [19,26,27,28].

LCQ is a 19-item validated specific QoL measure of cough over the period of previous two weeks [10]. Its scores can be calculated in 3 domains covering physical (8 items), psychological (7 items), and social (4 items) aspect of chronic cough, in addition to the total score. It evaluates the impact of cough on patients' QoL. It takes 5 to 10 minutes to complete. Scores are calculated by domain (range from 1 to 7) and then added to obtain the total score (range from 3 to 21), with higher scores indicating a better QoL. Our study group recently validated the Serbian version of the LCQ in sarcoidosis patients [29].

We measured QoL by standardized generic questionnaire – The fifteen-dimensional measure scale of health-related quality of life (15D) [18]. 15D is a multiatributive instrument for measurement of QoL that consists of 15 different and mutually exclusive health dimensions, each represented by one item. The total questionnaire score ranges between 0 and 1, where 1 signifies the highest level of QoL. 15D was used in different diseases in many different countries. The Serbian version of 15D was previously used in patients with sarcoidosis where it demonstrated good psychometric measurement properties [19,30].

On the same day subjects completed the questionnaires and performed pulmonary function tests – spirometry and the transfer factor of the lung for carbon monoxide (DLCO). Spirometry parameters included pre-bronchodilator forced expiratory vital capacity (FVC) and forced expiratory volume in one second (FEV_1), and it was measured with a pneumotachograph (Masterlab, Jaeger, Wurzburg, Germany). DLCO was measured using the single-breath method (Masterlab, Jaeger, Wurzburg, Germany). The European Respiratory Society criteria for lung function impairments was used [31].

Statistical methodology

Continuous variables are described by arithmetic mean and standard deviation, while nominal variables are presented by frequencies and percentages per respective outcomes. Chi-square test or the Exact probability test were used as univariate methods for testing the significance of difference between groups. The assessment of the relationship of sACE and other subjective characteristics of the health condition with cough-specific as well as generic QoL has been done by multivariate multiple linear regression (stepwise method). Stepping method criteria were based on the probability of F statistic, where variables with a probability less than 0.05 were retained, while variables with a probability greater than 0.10 were excluded from the model. The linearity assumption was checked by constructing a scatter plot for each independent variable. The diagnosis of collinearity between the predictors in the linear regression model was done by the arbitrary assessment of the conditional index and the variance inflation factor (VIF). The absence of the collinearity was defined by a conditional index less than 30 and VIF value less than 3 [32]. The Durbin-Watson statistic was used to arbitrarily evaluate the independence of the residuals. Homoscedasticity was graphically estimated based on the layout of the plot of standardized residuals vs. standardized predicted values. In the case of heteroscedasticity, a natural logarithm transformation of predictor variables was performed in order to homogenize the variance of the residuals. In order to normalize the distribution of residuals, all dependent variables were expressed by their squares. The normality of the distribution of residuals was verified by the Kolmogorov-Smirnov test. Outliers were detected and removed in each case where Cook's distance statistic was greater than 1.

The accepted level of significance was 0.05. The statistical analysis was conducted using IBM SPSS Statistics 20.

Results

Our study population consists of 275 patients with pulmonary sarcoidosis. The majority of them were females (65.5%). Tables 1 and 2 contain descriptive statistics for the total study population.

The total time required to complete all PRO questionnaires ranged from 30 to 40 minutes.

Multivariate multiple linear regression models for predictors of square transformed LCQ – Total and Domains Scores are presented in Table 3. There are four indipendent predictors of total cough-specific QoL. Natural logarithm of Borg and natural logarithm of DAL scores as well as natural logarithm of

Table 1. Descriptive statistics for continuous variables for the total study population (N = 275)

	Mean ± SD	Range
Age, years	50.13 ± 11.07	28 – 76
Height (cm)	168.85 ± 10.08	148 – 199
Weight (kg)	82.07 ± 16.46	42 – 145
Body-mass index (BMI, kg/m^2)	28.79 ± 5.33	16.00 – 55.25
Disease duration, years	15.62 ± 8.56	1 – 40
sACE (8 – 52 U/L)	47.35 ± 28.06	5.0 – 151.0
Dyspnea scores		
MRC	0.89 ± 0.69	0 – 3
Borg	1.45 ± 1.54	0 – 9
FAS Scores		
Total score	24.55 ± 6.23	15.00 – 42.00
Physical score	14.75 ± 3.08	8.00 – 22.00
Mental score	9.80 ± 4.06	5.00 – 23.00
DAL	3.00 ± 2.50	0 – 10
LCQ Scores		
Total score	16.94 ± 3.68	5.48 – 21.00
Physical domain score	5.48 ± 1.18	1.88 – 7.00
Psychological domain score	5.64 ± 1.29	1.86 – 7.00
Social domain score	5.82 ± 1.33	1.75 – 7.00
15D	0.85 ± 0.11	0.49 – 1.00
FEV_1 (% predicted)	99.60 ± 20.02	34 – 150
FVC (% predicted)	108.52 ± 17.40	41 – 156
FEV_1/FVC	76.57 ± 8.51	31.63 – 91.36
DLCO (% predicted)	81.55 ± 17.46	37 – 111

N = Numnber of patients; SD = standard deviation; sACE = Serum Angiotensin Converting Enzyme; MRC = Modified Medical Research Council Dyspnea Scale; Borg = Borg dyspnea category-ratio-10 scale; FAS = Fatigue Assessment Scale; DAL = List of Daily Activities; LCQ = Leicester Cough Questionnaire; 15D = Fifteen-dimensional measure of health-related quality of life; FEV_1 = Forced expiratory volume in one second; FVC = Forced expiratory vital capacity; PEF = Peak Expiratory Flow; DLCO = transfer factor of the lung for carbon monoxide

Tabela 2. Descriptive statistics for nominal variables for the total study population (N = 275)

Variable	F	%
Gender		
Men	95	34.5
Women	180	65.5
Age > 55 years		
Yes	173	62.9
No	102	37.1
Ro stage of lung disease		
0	68	24.7
1	148	53.8
2	47	17.1
3	12	4.3
Course of the sarcoidosis		
Acute	102	27.1
Chronic	173	62.9
Extrapulmonary sarcoidosis		
Yes	191	69.5
No	84	30.5
Treatment		
No treatment	17	6.2
Prednisone	98	35.6
Methotrexate	146	53.1
Chloroquine	5	1.8
Prednisone + Methotrexate	9	3.3
Smoking status		
Active smoker	25	9.1
Non-smoker	204	74.2
Ex-smoker	46	16.8
Total FAS score ≥ 22		
Yes	172	62.5
No	103	37.5

F = frequency; FAS = Fatigue Assessment Scale.

sACE values showed the strongest correlations with all square transformed LCQ scores. It was also the case with natural logarithm of Mental score of FAS that was not correlated only with LCQ Psychological domain score squared. All multivariate regression models obtained were linear and showed a good adequacy with respect to Durbin-Watson statistics (all individually were close to value of 2) – Table 3. Obtained plots of standardised residuals vs. standardised predicted values showed no obvious signs of funnelling, suggesting the assumption of homoscedasticity has been met (Figure 1). In the mentioned models, the Kolmogorov-Smirnov test showed that the values of the residuals were normally distributed ($p > 0.05$).

Parameters of multivariate multiple linear regression for predictors of generic QoL are given in

Table 3. Parametres of multivariate multiple linear regressions for predictors of LCQ – Total and Domains Scores

Model 1 – Dependent variable: LCQ - Total Score Square							
The total R^2 = 0.397 Durbin-Watson = 1.847	Unstandardized Coefficients		Standardized Coefficients	t	p	Change Statistics	
	B	SE	Beta			R^2 Change	p (F Change)
Constant	302.689	7.661		39.508	0.000	0.296	0.000 (78.865)
Ln (Borg Scale score)	-78.386	8.941	-0.544	-8.767	0.000		
Constant	353.819	15.158		23.342	0.000	0.053	0.000 (14.920)
Ln (Borg Scale score)	-58.229	10.076	-0.404	-5.779	0.000		
Ln (DAL score)	-47.874	12.394	-0.270	-3.863	0.000		
Constant	452.927	36.950		12.258	0.000	0.029	0.004 (8.581)
Ln (Borg Scale score)	-57.296	9.877	-0.398	-5.801	0.000		
Ln (DAL score)	-49.692	12.159	-0.280	-4.087	0.000		
Ln (sACE)	-26.798	9.148	-0.172	-2.929	0.004		
Constant	540.867	52.321		10.337	0.000	0.018	0.020 (5.503)
Ln (Borg Scale score)	-53.790	9.871	-0.373	-5.450	0.000		
Ln (DAL score)	-37.612	13.068	-0.212	-2.878	0.004		
Ln (sACE)	-25.750	9.048	-0.165	-2.846	0.005		
Ln (FAS mental score)	-47.073	20.067	-0.159	-2.346	0.020		
Model 2 – Dependent variable: LCQ - Physical Domain Score Square							
The total R^2 = 0.394 Durbin-Watson = 1.793	Unstandardized Coefficients		Standardized Coefficients	t	p	Change Statistics	
	B	SE	Beta			R^2 Change	p (F Change)
Constant	31.252	0.782		39.971	0.000	0.289	0.000 (74.972)
Ln (Borg Scale score)	-7.887	0.911	-0.538	-8.659	0.000		
Constant	37.088	1.528		24.270	0.000	0.067	0.000 (19.146)
Ln (Borg Scale score)	-5.599	1.014	-0.382	-5.521	0.000		
Ln (DAL score)	-5.470	1.250	-0.303	-4.376	0.000		
Constant	45.370	3.762		12.061	0.000	0.020	0.017 (5.777)
Ln (Borg Scale score)	-5.512	1.002	-0.376	-5.502	0.000		
Ln (DAL score)	-5.630	1.236	-0.312	-4.555	0.000		
Ln (sACE)	-2.237	0.931	-0.141	-2.404	0.017		
Constant	54.106	5.331		10.149	0.000	0.018	0.023 (5.230)
Ln (Borg Scale score)	-5.164	1.002	-0.352	-5.154	0.000		
Ln (DAL score)	-4.429	1.330	-0.245	-3.330	0.001		
Ln (sACE)	-2.133	0.921	-0.134	-2.316	0.022		
Ln (FAS mental score)	-4.676	2.045	-0.155	-2.287	0.023		
Model 3 – Dependent variable: LCQ - Psychological Domain Score Square							
The total R^2 = 0.329 Durbin-Watson = 1.886	Unstandardized Coefficients		Standardized Coefficients	t	p	Change Statistics	
	B	SE	Beta			R^2 Change	p (F Change)
Constant	33.967	0.932		36.449	0.000	0.259	0.000 (64.371)
Ln(Borg Scale score)	-8.710	1.086	-0.509	-8.023	0.000		

Model 3 – Dependent variable: LCQ - Psychological Domain Score Square							
Constant	39.043	1.865		20.930	0.000	0.037	0.002 (9.723)
Ln (Borg Scale score)	-6.720	1.238	-0.393	-5.428	0.000		
Ln (DAL score)	-4.758	1.526	-0.226	-3.118	0.002		
Constant	51.463	4.555		11.299	0.000	0.033	0.003 (8.861)
Ln (Borg Scale score)	-6.590	1.213	-0.385	-5.432	0.000		
Ln (DAL score)	-4.998	1.496	-0.237	-3.340	0.001		
Ln (sACE)	-3.354	1.127	-0.181	-2.977	0.003		
Model 4 – Dependent variable: LCQ - Social Domain Score Square							
The total R^2 = 0.348 Durbin-Watson = 1.854	Unstandardized Coefficients		Standardized Coefficients	t	p	Change Statistics	
	B	SE	Beta			R^2 Change	p (F Change)
Constant	36.256	0.998	-0.494	36.324	0.000	0.244	0.000 (59.399)
Ln (Borg Scale score)	-8.961	1.163		-7.707	0.000		
Constant	42.951	1.970	-0.349	21.799	0.000	0.058	0.000 (15.159)
Ln (Borg Scale score)	-6.337	1.308	-0.281	-4.846	0.000		
Ln (DAL score)	-6.276	1.612		-3.894	0.000		
Constant	56.388	5.533	-0.321	10.191	0.000	0.025	0.010 (6.724)
Ln (Borg Scale score)	-5.819	1.303	-0.202	-4.466	0.000		
Ln (DAL score)	-4.517	1.726	-0.185	-2.617	0.010		
Ln (FAS mental score)	-6.890	2.657		-2.593	0.010		
Constant	66.305	6.846	-0.316	9.685	0.000	0.021	0.017 (5.771)
Ln (Borg Scale score)	-5.732	1.287	-0.215	-4.454	0.000		
Ln (DAL score)	-4.799	1.708	-0.177	-2.810	0.005		
Ln (FAS mental score)	-6.579	2.626	-0.145	-2.505	0.013		
Ln (sACE)	-2.842	1.183		-2.402	0.017		

Ln = Natural logarithm; sACE = Serum Angiotensin Converting Enzyme; Borg = Borg dyspnea category-ratio-10 scale; FAS = Fatigue Assessment Scale; DAL = List of Daily Activities; LCQ = Leicester Cough Questionnaire; SE = Standard Error

Table 4. 15D score square significantly correlated with four independent predictors. It negatively correlated with the MRC and natural logarithm of FAS Total scores. On the other side, it positively correlated with natural logarithm of LCQ Physical Domain Score. This linear model also showed good adequacy characteristics (Durbin-Watson statistic = 1.844), the variance of the residuals was constant (Figure 1) and the values of the residuals were normally distributed (Kolmogorov-Smirnov statistic = 0.064; p = 0.058).

We did not notice significant relationship between pulmonary function parameters (FEV_1, FVC, FEV_1/FVC, DLCO) and QoL scores.

Discussion

Evaluation of PROs is very important in chronic diseases like sarcoidosis where objective outcomes cannot fully direct physicians in therapeutic decision making and follow up of their patients. It was previously recognized that potential endpoints in sarcoidosis research should include: QoL measures, symptoms of cough, dyspnea, and wheeze, the frequency of disease exacerbations (requiring corticosteroid bursts or additional anti-sarcoidosis therapy), and corticosteroid-sparing effects of interventions [33,34]. In addition, Moor and coauthors recently

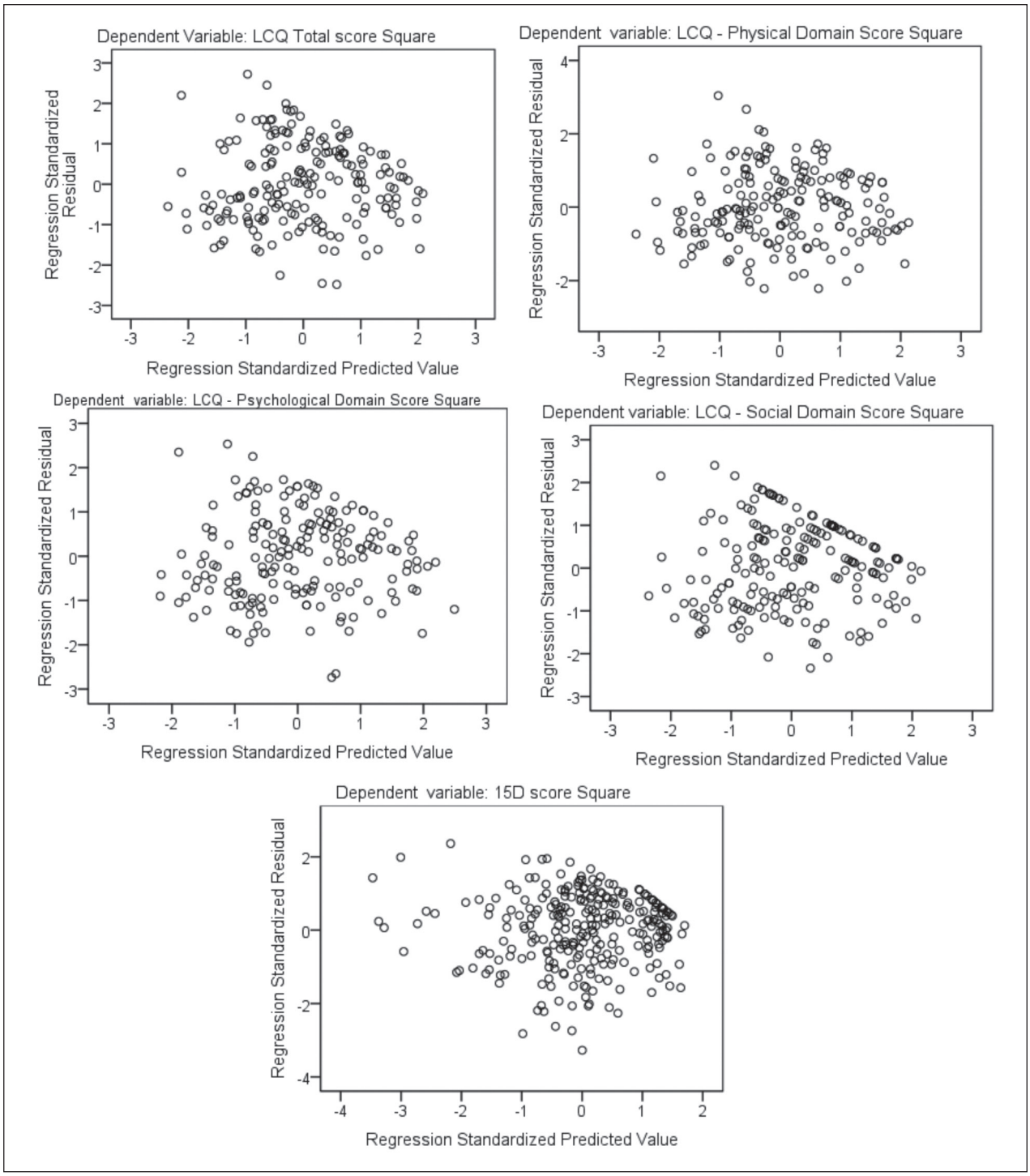

Fig. 1. Scatterplots of standardised residuals vs. standardised predicted values for LCQ – Total and Domains Scores and 15D Score
LCQ = Leicester Cough Questionnaire; 15D = Fifteen-dimensional measure of health-related quality of life

Table 4. Parameters of multivariate multiple linear regression for predictors of 15D Score

Dependent variable: 15D Score Square							
The total R^2 = 0.633 **Durbin-Watson = 1.808**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	**p**	**Change Statistics**	
	B	**SE**	**Beta**			**R^2 Change**	**p (F Change)**
Constant	0.907	0.013		70.682	0.000	0.512	0.000 (280.233)
MRC score	-0.191	0.011	-0.716	-16.740	0.000		
Constant	1.663	0.102		16.331	0.000	0.085	0.000 (55.820)
MRC score	-0.146	0.012	-0.546	-12.127	0.000		
Ln (FAS total score)	-0.251	0.034	-0.337	-7.471	0.000		
Constant	1.225	0.130		9.412	0.000	0.036	0.000 (25.866)
MRC score	-0.117	0.013	-0.439	-9.156	0.000		
Ln (FAS total score)	-0.211	0.033	-0.282	-6.363	0.000		
Ln (LCQ - Physical Domain Score)	0.171	0.034	0.237	5.086	0.000		

Ln = Natural logarithm; FAS = Fatigue Assessment Scale; LCQ = Leicester Cough Questionnaire; 15D = Fifteen-dimensional measure of health-related quality of life; MRC = Modified Medical Research Council Dyspnea Scale; SE = Standard Error

evaluated the needs and perceptions of patients with sarcoidosis and their partners and demonstrated that 40% of sarcoidosis patients identified fatigue as their most disabling symptom, followed by painful joint/muscles (20%) and dyspnea (15%). Cough and ocular symptoms followed by frequency of 10% [35].

In this study we assessed significant predictors of both cough-specific and generic Qol in patients with pulmonary sarcoidosis.

We noticed that dyspnea was the strongest predictor of cough-specific and generic QoL in our study population. Increased natural logarithm of Borg dyspnea scores had the biggest negative influence on all almost every cough-specific QoL domains scores square and the highest correlation was noticed with the total LCQ score square (B = -57.296, $p < 0.001$). On the other side, dyspnea measured by MRC score was the strongest predictor of generic QoL score square (B = -0.117, $p < 0.001$). Hinz and coauthors showed that dyspnea is an important symptom in the prediction of anxiety and depression in sarcoidosis patients [36].

It has been previously demonstrated that impaired exercise tolerance, fatigue and muscle weakness appeared to have a negative influence on the QoL of patients with sarcoidosis [37,38]. In our study we obtained similar results regarding the influence of fatigue, as common symptom of sarcoidosis, on both cough-specific and generic QoL. Mental aspect of patients' fatigue significantly correlated with all LCQ domains except with psychological QoL domain, while total FAS score was significant predictor of generic QoL. It is very important to stress here that the LCQ is not synonymous with cough but rather it is a cough QoL PRO. So, the fatigue itself may not worsen cough but worsen the effect of cough on the patient's QoL.

Physical activity offers great health benefits for a wide range of conditions. Hendriks at al recently evaluated the self-reported experiences with physical activity among 233 patients with sarcoidosis [39]. Most patients emphasized that exercise and physical activity was beneficial to them. In our study limitation of daily activities, as assessed by DAL, significantly influenced all domains of cough-specific QoL but it did not predict the generic QoL.

Among the spectrum of subjective QoL predictors, sACE was the only objective disease outcome that significantly influenced all domains of cough-specific QoL. Serum ACE has been the most frequently used laboratory test in sarcoidosis. It is produced by epithelioid cells derived from recently-activated macrophages in granulomas and it is a well-known marker for sarcoidosis activity. The enzyme is also supposed to give indication of total body granuloma burden (not ones found in the lungs only) [40] and disease severity [41], although the clinical value of this marker is still under debate as results of different

studies are conflicting [42]. Yasar and coauthors showed that serum ACE was a predictor of extrathoracic involvement of sarcoidosis [43]. We have recently demonstrated that severity of cough in sarcoidosis correlated with the disease activity as measured by the concentration of sACE [44]. In our study natural logarithm of sACE was independent predictor of all cough-specific QoL domains in a negative direction, i.e. its lower values indicated reduced cough perception and a better QoL. The degree of these correlations is generally low and the most prominent impact sACE had on the total LCQ scores (B = -25.750, p = 0.005, Table 3). According to the available information, we are the first who demonstrated the impact of disease activity, as measured by sACE, on the cough-specific and generic QoL in sarcoidosis patients, together with other subjective outcomes like dyspnea, fatigue and limitation of daily activities.

Regarding the generic QoL, measured by 15D, we obtained its different predictors. Dyspnea measured by MRC scale, overall fatigue (as assessed by total FAS score) and physical domain of LCQ were significant predictors of patients' generic QoL. We showed that dyspnea determines generic QoL (R^2 change = 0.512) significantly more than physical domain of LCQ (R^2 change = 0.036) and fatigue (R^2 change = 0.085) – Table 4. This might indicate that psychological and social domains of LCQ measure QoL aspects which are not covered by the 15D instrument emphasizing the importance not only to use the generic QoL questionnaire, but also the LCQ in sarcoidosis patients. Although the disease activity measured by the sACE was not a significant predictor of generic QoL in our study group, it still can indirectly affect it in sarcoidosis patients by influencing physical domain of cough-specific QoL that was significant predictor of generic QoL. Therefore, we suggest that antitussives should be considered in the treatment of chronic cough in sarcoidosis since it can influence improvement of overall QoL without safety risks of masking the symptomatology caused by increasing of disease activity, since we demonstrated a weak correlation between the cough-specific QoL and disease activity.

We confirmed that the LCQ provides a significant contribution in measurement and understanding of complex relationships between the disease activity, dyspnea, limitation of daily activities, fatigue, cough-specific and overall QoL of sarcoidosis patients. In other published studies [45-48] correlations between LCQ scores and different PROs (mainly generic QoL instruments) were mostly moderate as it was also the case with the original LCQ validation [10]. In the process of validation of the German version of the LCQ (among 200 sarcoidosis patients), Schupp and coauthors demonstrated only a moderate correlation of LCQ scores with generic and respiratory-specific QoL questionnaires (SF-36, Borg, VAS Dyspnea) [12]. The Physical Component Summary Score of the SF-36 showed a quite high correlation with the LCQ, while the Mental Component Summary Score did not.

Altlhough our patients were fatigued, had significant dyspnea, perceived limitations in their physical activities, and had a poor QoL, they had normal pulmonary function. This is in line with results of previous studies demonstrating that pulmonary function testing cannot function as a surrogate for these other parameters and cannot be used to assess the overall health of sarcoidosis patients [49-50]. All pulmonary function parameters in our study have not been significantly correlated with both LCQ and 15D scores. Judson et al found that cough was not statistically significantly different in terms of spirometric measures (FEV_1%, FVC% and FEV_1/FVC) [11].

A major limitation of this study is that the data were collected in a tertiary health-care setting, i.e. a specialised referral clinic for sarcoidosis patients. This means that our patients had predominantly severe forms of the disease and the scores for all patient reported outcomes were probably more severe than for the average sarcoidosis patient. Therefore, our results may not be generalizable to patients in primary care settings. In addition, 40% of our study patients were receiving oral corticosteroid therapy, and this may have had a postive or negative impact upon their health status and other measured variables like sACE. Namely, corticosteroid medications may reduce sACE levels [51] and indirectly influence cough-specific QoL. Moreover, corticosteroids should improve cough and therefore improve QoL on that basis. However, corticosteroids may worsen QoL on the basis of their numerous side effects. Besides that, we did not measure the frequency of coughing in our study group and sarcoidosis patients were included regardless of the presence of cough. Overrall, the predictors evaluated suit general QOL better and therefore only a limited assessment of

cough was possible. Finally, important limitation of our study is that we did not record the use of ACE inhibitors in our study population, which may have reduced sACE levels [52] or cause a dry, debilitating cough [53]. On the other hand, several nominal or ordinal variables that could potentially affect cough [gender, smoking, radiology variables (extent, fibrosis, consolidation, PET active), multiorgan disease, immunosuppressive drugs, reflux, rhinitis], could not be used in our linear regression models. Nominal or ordinal variables (even if they prove significant) impair the linearity of the regression model and make it inadequate, as well as lead to the failure to fulfill other assumptions for accepting it (normality of residual distribution and constant residual variance).

We conclude that increase of disease activity as measured by sACE, together with increased dyspnea and mental fatigue component as well as limited daily activities, significantly influences deterioration of the cough-specific QoL in sarcoidosis patients. In addition, disease activity indirectly impacts overall QoL by decreasing physical domain of cough-specific QoL that is correlated to generic QoL. In order to improve overall QoL, we suggest that chronic cough in sarcoidosis should be treated with antitussives without safety risks of masking the symptomatology caused by increased disease activity. It is important to measure both cough-specific and generic QoL in sarcoidosis patients since they measure different health aspects and their predictors can be different.

Conflict of interest statement: None of the authors disclosed any potential conflicts of interest

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2);169-179 DOI: 10.36141/svdld.v37i2.9169

Obstructive sleep apnea in sarcoidosis and impact of CPAP treatment on fatigue

Pier-Valerio Mari[1,2], Giuliana Pasciuto[1,2], Matteo Siciliano[1,2], Jacopo Simonetti[1,2], Federico Ballacci[2], Francesco Macagno[1,2], Bruno Iovene[1], Filippo Martone[3], Giuseppe Maria Corbo[1,2], Luca Richeldi[1,2]

[1] Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome (Italy); [2] Università Cattolica del Sacro Cuore; [3] Amici Contro La Sarcoidosi Italia ONLUS

Abstract. *Rationale:* An increased incidence of Obstructive Sleep Apnea (OSA) in sarcoidosis has been described in small sample size studies. Fatigue is common in sarcoidosis and OSA could be a relevant, treatable comorbidity. To date, the effect of Continuous Positive Airway Pressure (CPAP) on fatigue has never been assessed. *Objectives:* To investigate the prevalence of OSA in sarcoidosis, fatigue status and daytime sleepiness in patients of our center. To explore the effect of CPAP in fatigue and daytime sleepiness after 3 months using validated questionnaires. *Method:* Single group, one center, open-label prospective cohort study. *Measurements and main result:* We enrolled 68 patients and OSA was diagnosed in 60 (88.2%): 25 (36.8%) were mild while 35 (51.5%) were moderate-to-severe. 38 (55.9%) patients received CPAP but only 20 (30.9%) were compliant at 3-month evaluation. Questionnaires demonstrated fatigue in 34 (50%) and daytime sleepiness in 21 (30.9%). In multivariate regression analysis, Scadding stage and FAS behave as predictors of Apnea-Hypopnea Index (AHI) severity while sleepiness and steroids weren't associated. FAS score (Δ_{FAS} = 6.3; p = 0.001) and ESS score (Δ_{ESS} = 2.8; p = 0.005) improved after three months of CPAP. *Conclusions:* OSA is highly prevalent in patients affected by sarcoidosis. ESS questionnaire is not reliable for OSA screening and other pre-test probability tool should be evaluated in further studies. CPAP leads to a significative reduction of fatigue and daytime sleepiness at three-month. Further studies are needed to confirm the high prevalence of OSA in sarcoidosis and the positive role of CPAP in fatigue. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 169-178)*

Key words: Sarcoidosis; Sleep Apnea; CPAP

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Correspondence: Mari Pier-Valerio,
MD (ORC-ID: 0000-0002-3307-217X)
Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
Largo Agostino Gemelli, 8
Rome (IT) 00168
E-mail: piervalerio.mari@gmail.com

Introduction

Sarcoidosis is a granulomatous disease characterized by a great heterogeneity in clinical presentation, in the disease course and therapeutic results. Pathogenesis is still unclear; exaggerated immune response to unidentified antigens is thought to be the key pathogenic mechanism[1]. Sarcoidosis is a worldwide disease but prevalence is higher in the northern European and African-American populations[2]. Involvement of lung parenchyma and thoracic lymphadenopathies are very common features[3].

An increased incidence of Sleep-disordered Breathing (SDB) and Obstructive Sleep Apnea (OSA) has been observed in patients affected by sarcoidosis though the pathogenesis is still unclear[4].

OSA is a disorder of upper airways collapse during sleep time leading to oxygen desaturation, sleep fragmentation and hypercapnia[5]. Moreover, once the obstruction has taken place, an arousal from sleep is induced by a respiratory effort allowing hyperventilation to occur[6]. Thus, arousals prevent asphyxia during upper airway obstructions but can lead to cardiovascular activation and contribute to adverse events of sleep apneas. Such condition is common, and recent studies suggest a significant prevalence of moderate-to-severe disordered breathing in high-income countries[7] of 49.7% in men and 23.4% in women[8]. Obstructive Sleep Apnea (OSA) is defined by an Apnea-Hypopnea Index (AHI) more than five and the collapse leads to a fall of blood saturation during sleep linked to daytime sleepiness, and stroke[9,10]. Patients with sleep apneas report excessive daytime sleepiness, non-restorative sleep and fatigue. Continuous positive airway pressure (CPAP) is the treatment of choice since the first publication in 1981[11] in moderate-to-severe OSA syndrome although mild diseases may be allocated to treatment.

The association between OSA and sarcoidosis is nowadays without a clear pathogenesis explanation. Upper airway collapsibility might play a key role in pathogenesis of OSA in Interstitial Lung Diseases. A restrictive pattern on pulmonary function test leads to an increased airway collapsibility due to the caudal traction on these structures[12]. Also, a high Body Mass Index with deposition of fat around upper airways may enhance the collapsibility. More hypotheses have been proposed: sarcoid neuropathy, obesity due to steroids and upper airway resistance secondary to airway disease[4,13]. A higher OSA prevalence was found in subjects with lupus pernio and increased AHI was reported among patients with lung parenchymal involvement[14]. In addition to the OSA, sarcoidosis is frequently associated with fatigue, a state of physical and mental weariness[15] as a consequence of inflammatory mediators[16]. Fatigue is common with 50-70% prevalence in patients affected by sarcoidosis[17]. Regardless of its underlying cause, fatigue has a great impact on the life of patients affected with sarcoidosis and questionnaires such as the Fatigue Assessment Scale (FAS) have been validated[18] and used in clinical practice in order to assess the burden of such condition.

Up-to-date, poor data is available on the prevalence of OSA in Sarcoidosis and no data is neither available about the effect of obstructive sleep apnea treatment with CPAP device on sarcoidosis nor the effect on the fatigue state assessed with FAS questionnaire.

Therefore, we aimed to define the prevalence of OSA in patients from our Sarcoidosis Clinic and to explore the effects on fatigue due to the treatment of OSA with CPAP.

Methods

The SARCOIDOSAS study is a single group, open labeled prospective cohort study conducted in Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma (Italy). The trial was approved by the Institutional Board Review (ID **2455**, approved on 05 April 2019; principal investigator: R. L) and have been registered on ClinicalTrials.gov (SARCOIDOSAS number, **NCT03926832**, registered 10 April; principal investigator: M. PV). Patients affected by sarcoidosis older than 18 years to a maximum of 85 years were eligible in the Sarcoidosis Clinic of our institution: a reference, tertiary care center for rare interstitial lung diseases. All patient met ATS criteria[1] for diagnosis and had a histology-proven sarcoidosis. The exclusion criteria included: ongoing CPAP treatment or having a diagnosis of psychiatric disorders. We contacted (telephone / mail) the whole cohort of our Sarcoidosis Clinic (n = 122 patients) but only 84 (68.9%) gave back us a feedback after the contact. Contacted patients were addressed for a first eligibility evaluation and enrolled between April and May 2019. All participants provided informed

consent. We did not impose criteria to select patients with higher probability of diagnosing sleep apnea syndrome. Furthermore, patients with OSA diagnosis[19] were allocated to treatment according to the latest American Academy of Sleep Medicine (AASM)[20]: Continuous Positive Airway Pressure (CPAP) therapy was started in all those with a moderate-to-severe OSA and in those with mild OSA with a documented symptoms of excessive daytime sleepiness or history of insomnia or hypertension/ischemic heart disease or history of stroke.

Baseline evaluation

After the initial screening of the entire cohort of our Sarcoidosis Clinic, a total of 84 subjects were eligible but 16 of them declined to participate in the study. Thus, 68 patients were recruited and performed a baseline evaluation collecting data about demographic, Scadding stage on chest x-ray and corticosteroid treatment. Lung function tests of the cohort were collected including the following parameters: Forced Vital Capacity (FVC), Total Lung Capacity (TLC) and Diffusing Capacity divided by the Alveolar Volume (DL_{CO}/Va). Moreover, fatigue status and daytime sleepiness were assessed by completing the Fatigue Assessment Scale (FAS) and Epworth Sleepiness Scale (ESS) questionnaires. The FAS is a 10-item validated questionnaire to assess the fatigue in patients affected by sarcoidosis ranging from 10 to 50 points while the ESS determines the likelihood of falling asleep during various scenarios for a total score from 0 to 24. Fatigue was determined if FAS ≥ 22 and extreme fatigue status if FAS ≥ 35 points while daytime sleepiness was established if ESS > 10 points. Both FAS and ESS questionnaires were administered via face-to-face interview during the same baseline or follow up medical evaluation. Regardless of the result of the screening questionnaires, all patients scheduled an overnight home sleep study using a level III portable diagnostic device (VitalNight Plus®, VitalAire®, Milan, Italy). The following parameters were measured: airflow measured by thermistor and nasal pressure cannula, thoracoabdominal respiratory bands, pulse oximetry and body position. Obstructive sleep apnea syndrome was identified when apnea/hypopnea index (AHI) was found more than five events per hour during the night sleep study. Sleep studies were automatically analyzed and then rescored using a manual editing of the total recording time. OSA severity was determined using the rescored apnea/hypopnea index (AHI) according to the following grading score: mild (5 ≥ AHI > 15), moderate (15 ≥ AHI > 30), severe (AHI ≥ 30). All moderate-to-severe patients, along with those with mild OSA that have excessive daytime sleepiness or cardiovascular disease, were allocated to treatment. An autoset device was given with a pressure range between 8.0 and 15.0 cm H2O (AirSense 10 AutoSet®, Resmed®) in order to start a CPAP treatment.

Three-month follow-up

Patients that WERE allocated to treatment were evaluated after three months of CPAP therapy: fatigue status and daytime sleepiness were newly assessed and change from baseline to 90 days were collected. The minimal important difference (MID) in the change of FAS (Δ_{FAS}) is defined as a reduction of at least 4 points or 10% of the baseline value, while the MID in the change of ESS (Δ_{ESS}) is a reduction of at least 2 points of the baseline value. Also, compliance to CPAP therapy was evaluated by reading the device report and threshold of "good" compliance was defined as device use for more than 4 hours per night and at least 70% of total number of nights.

Statistical analysis

We analyzed the OSA prevalence in our Sarcoidosis Clinic. The sample was described using descriptive statistics techniques. Quantitative variables were summarized using means ± standard deviation; categorical variables presented using (absolute and percentage) frequency tables. The strength of associations was assessed using Chi-Squared test (categorical variables) or Pearson correlation coefficient (continuous variables). Apnea-Hypopnea Index potentially independent predictors were investigated *post hoc* by using multiple linear regression analysis. Statistical results were adjusted for potential confounding variables. Correlation between baseline and follow up outcomes were assessed using a paired T-Test after being tested for normality. SAS version 9.4 or higher statistical software was used (SAS Institute Inc®, Cary, North Carolina, USA).

Results

Baseline characteristics

The flowchart diagram of the study is presented in Figure 1. We enrolled 68 patients and the cohort was predominantly female in 42 (61.8%). Mean age was 60.2 ± 10.0 SD along with a mean BMI of 27.9 ± 5.1 SD. 32 (50.0%) were former smokers with a mean pack/year of 8.8 ± 9.4 SD. Baseline lung function tests did show FVC % 108.6 ± 17.6 SD, TLC % 98.2 ± 13.1 SD and DLCO % 91.2 ± 16. We also defined Sarcoidosis staging on the chest radiograph: stage 0-I was identified in 28 (41.2%), stage II-III in 38 (55.9%) while stage IV in only 2 (2.9%). Corticosteroid therapy was confirmed in 31 (45.6%) and 26 (38.2%) were treated for more than three months with steroids.

Fatigue and daytime sleepiness

Fatigue status and daytime sleepiness were found to be common in our cohort: the FAS questionnaire assessed a mean FAS of 24.8 ± 9.7 SD, the fatigue status in 34 (50.0%) and an extreme fatigue status in 15 (22.1%), while the ESS questionnaire

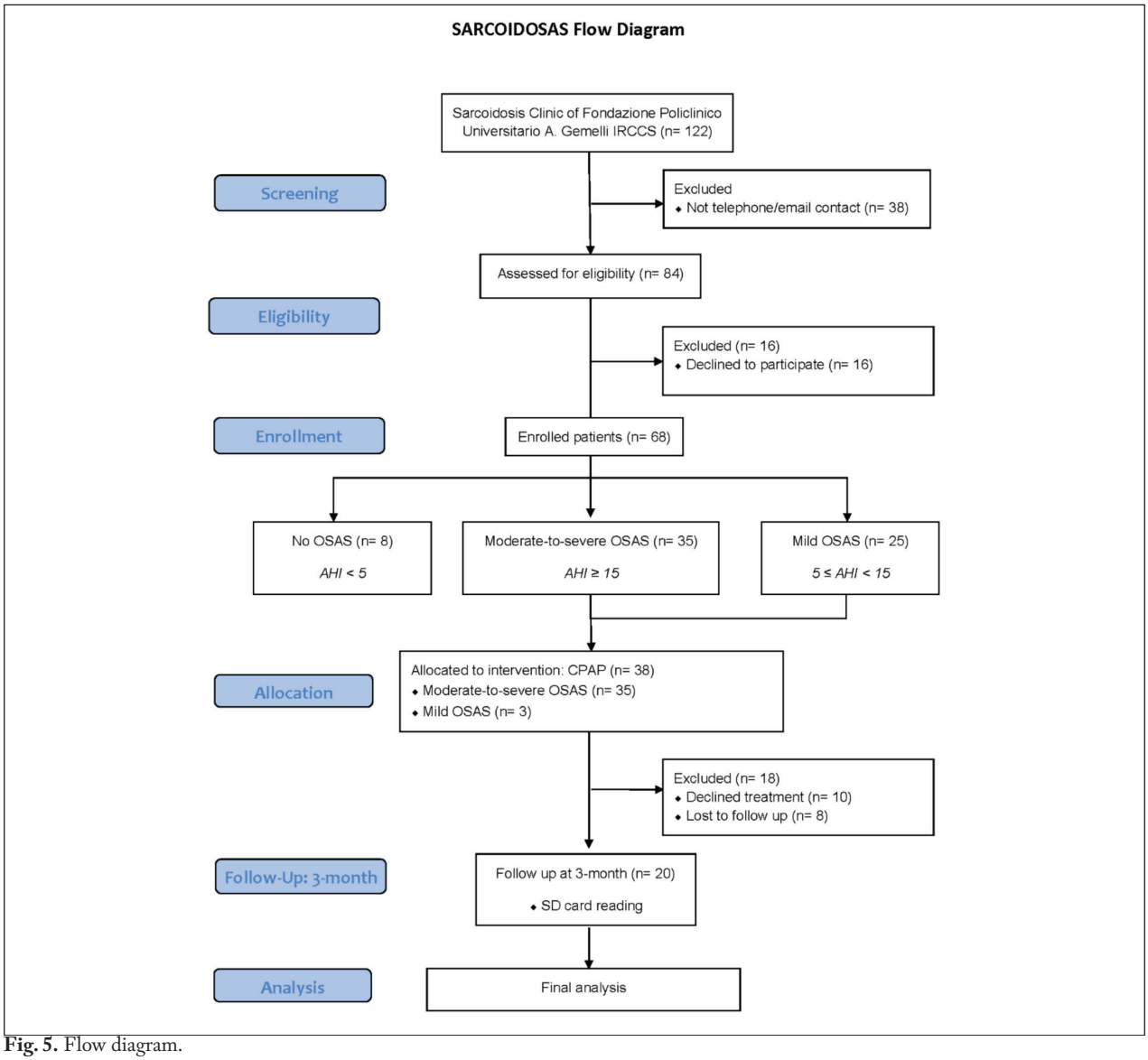

Fig. 5. Flow diagram.

did show a mean ESS of 7.9 ± 5.2 and the presence of daytime sleepiness in 21 (30.9%). Moreover, the baseline FAS score did show a negative correlation with male gender (coefficient B: -8.8; p = 0.0001) and correlate with ESS score at baseline (coefficient B: 0.74; p = 0.001).

Prevalence and severity of OSA

OSA was prevalent in the Sarcoidosis Clinic of our center and was diagnosed in 60 (88.2%): 25 (36.8%) had a mild grade and 35 (51.5%) were moderate-to-severe. CPAP was proposed according to AASM guidelines to all the moderate-to-severe patients (n = 35) and some of the mild group (n = 3 with history of ischemic heart disease) allocating a total of 38 (55.9%) patients to treatment. Table 1 describes the demographic and clinical characteristics of the groups.

Association between AHI and Baseline evaluation

AHI did show a negative, weak correlation with questionnaires results of FAS and ESS. The regression plots in Figure 2 illustrate the negative correlation coefficient (ρ) when AHI was compared to FAS (ρ: -0.31, p = 0.009) and ESS (ρ: -0.32, p = 0.007) at baseline. Also, TLC% predicted seems to be negatively correlated to AHI (ρ: -0.47, p = 0.001) along with FVC% predicted (ρ: -0.34, p = 0.015), while a positive, moderate correlation was established with weight (ρ: 0.49, p = 0.001) and BMI (ρ: 0.41, p = 0.001). The *post hoc* regression analysis (Table 2) adjusted for multiple variables (male gender, BMI, advanced Scadding stages, FAS/ESS at baseline, treatment with corticosteroids for more than 3 months at baseline) revealed some interesting insights. In this model, BMI, Scadding stage and FAS score behave as independent predictors of Apnea-Hypopnea Index

Table 1. Demographic and clinical characteristics by OSA severity

Characteristic	None	Mild	Moderate-to-Severe	P value
Subjects, n (%)	8 (11.8%)	25 (36.7%)	35 (51.5%)	
Age in years, mean ± SD	53.2 ± 5.7	61.5 ± 10.5	61.0 ± 10.1	NS
Gender, n				
Female	7	18	17	
Male	1	7	18	**0.050**
Anthropometrics, mean ± SD				
Height, meters	1.58 ± 0.01	1.63 ± 0.01	1.65 ± 0.01	NS
Weight, Kilograms	65.9 ± 21.2	70.5 ± 10.6	80.7 ± 14.2	**0.0045**
BMI	26.2 ± 8.3	26.2 ± 3.1	29.5 ± 5.1	**0.0302**
Lung Function Test, % ± SD				
FVC	105.4 ± 17.7	114.2 ± 16.9	105 ± 17.8	NS
TLC	97.4 ± 14.2	106.9 ± 10.4	92.1 ± 11.3	**0.0010**
DLCO/Va	79.0 ± 12.4	91.2 ± 18.3	94.8 ± 15.2	NS
Smoke, n (%)				
Ever smoker	5 (7.3%)	12 (17.6%)	15 (22.1%)	NS
Never smoker	3 (4.4%)	13 (19.2%)	20 (29.4%)	
Extrapulmonary involvement, n (%)				
No	7 (10.3%)	13 (19.2%)	18 (26.4%)	
Yes	1 (1.5%)	12 (17.6%)	17 (25.0%)	NS
Scadding stage, n (%)				
0-I	4 (5.9%)	11 (16.2%)	13 (19.1%)	
II-III-IV	4 (5.9%)	14 (20.5%)	22 (32.4%)	NS
Corticosteroids at baseline, n (%)				
No	6 (8.8%)	15 (22.1%)	16 (23.5%)	
Yes	2 (2.9%)	10 (14.8%)	19 (27.9%)	NS
FAS baseline score, mean ± SD	28.9 ± 9.3	26.2 ± 8.9	22.8 ± 10.1	0.18
ESS baseline score, mean ± SD	10.9 ± 7.2	8.9 ± 5.1	6.6 ± 4.4	0.055

BMI = Body Mass Index, FVC = Forced Vital Capacity, TLC = Total Lung Capacity, DLCO/Va = Diffusing Capacity / Alveolar Volume, FAS = Fatigue Assessment Scale, ESS = Epworth Sleepiness Scale, NS = Not significant

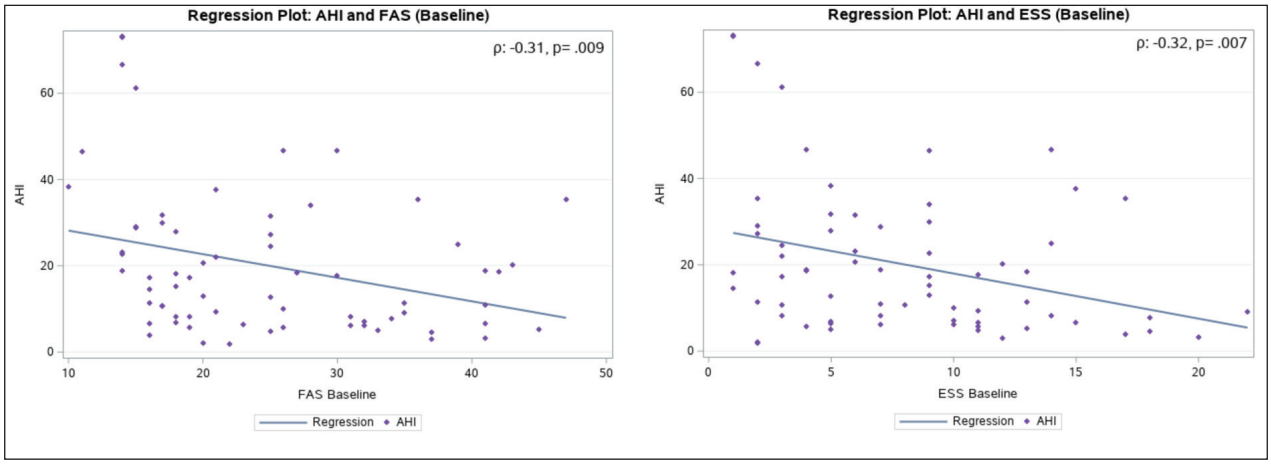

Fig. 2. Regression plot: FAS, ESS and AHI. FAS: Fatigue Assessment Scale, ESS: Epworth Sleepiness Scale, AHI: Apnea-Hypopnea Index, ρ: Pearson correlation coefficient.

Table 2. Regression analysis summary for independent predictors of AHI

	Unadjusted			Adjusted*		
Variable	**B (95% CI)**	**t**	**P>|t|**	**B (95% CI)**	**t**	**P>|t|**
Male gender	8.0 (-0.2-16.3)	1.94	0.056	10.2 (-0.1-20.1)	2.02	**0.050**
BMI	1.3 (0.6-2.0)	3.55	0.001	1.4 (0.6-2.2)	3.54	**0.001**
Scadding stages II-III-IV	5.6 (-2.7-13.8)	1.35	0.183	6.3 (-1.5-17.3)	2.04	**0.048**
TLC	-0.7 (-1-0.3)	-3.65	0.001	-0.5 (-0.8-0.2)	-2.83	**0.007**
FAS Baseline	-0.5 (-0.9-0.1)	-2.68	0.009	0.1 (-0.5-0.6)	0.11	0.916
ESS Baseline	-1.0 (-1.8-0.3)	-2.76	0.007	-1.1 (-1.9-0.2)	-2.40	**0.021**
Steroid treatment > 3m	5.2 (-3.0-13.4)	1.27	0.208	0.1 (-8.7-9.2)	0.03	0.997

*Adjusted R-squared: 0.47
AHI = Apnea-Hypopnea Index, BMI = Body Mass Index, CI: 95% Confidence Interval of Coefficient (B), ESS = Epworth Sleepiness Scale, FAS = Fatigue Assessment Scale, "m" = months, TLC = Total Lung Capacity.

severity while other covariates such as ESS score and steroids at baseline seems to be not related to AHI prediction. These results confirmed the known role of BMI along with the male gender in predicting severity of AHI but also enlightened that radiological impairment in sarcoidosis is associated to the OSA severity. Furthermore, the therapy with corticosteroids for more than 3 months in patients evaluated at baseline was not predictive of the AHI severity as described in the multiple regression analysis.

Three-month evaluation

An evaluation after three months since the CPAP start was obtained and 20 (29.4%) patients were analyzed. The follow-up questionnaires (FAS_{90} and ESS_{90}) investigate fatigue and daytime sleepiness after CPAP treatment using the same items of the baseline questionnaires: FAS_{90} had a mean of 18.7 ± 8.6 SD while ESS_{90} was 4.0 ± 2.8 SD. Changes in FAS and ESS questionnaires score from baseline to 90-day are shown in Figure 3 and confirmed an improvement of fatigue and sleepiness: the change in FAS (Δ_{FAS}) was 6.3, 95% CI 4.7-8.9, p = 0.001 and the change in ESS (Δ_{ESS}) was 2.8, 95% CI 2.3-4.5, p = 0.005. CPAP adherence tracking data were analysed using the device's SD card. Compliance to treatment was good in 13 (65.0%) with a mean AHI residual of 3.4 ± 5.1 SD and a percentage of used days > 4 hours of 65% ± 34.7 SD. The explorative analysis shows that only good adherence to CPAP treatment (Figure 4) reduced fatigue (7.5, 95% CI

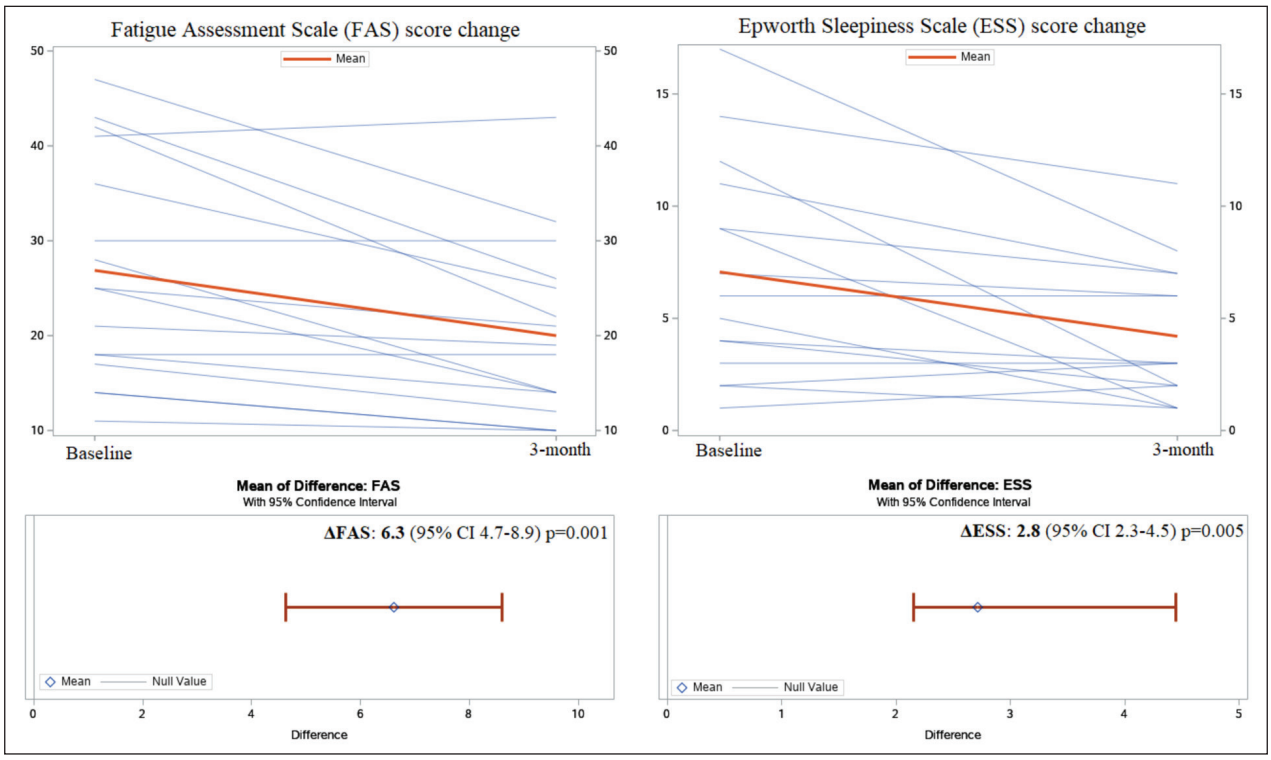

Fig. 3. Changing in FAS and ESS questionnaires score from baseline to 3-month. FAS: Fatigue Assessment Scale, ESS: Epworth Sleepiness Scale, Δ_{FAS}: Difference between baseline FAS and FAS at 3-month, Δ_{ESS}: Difference between baseline ESS and ESS at 3-month.

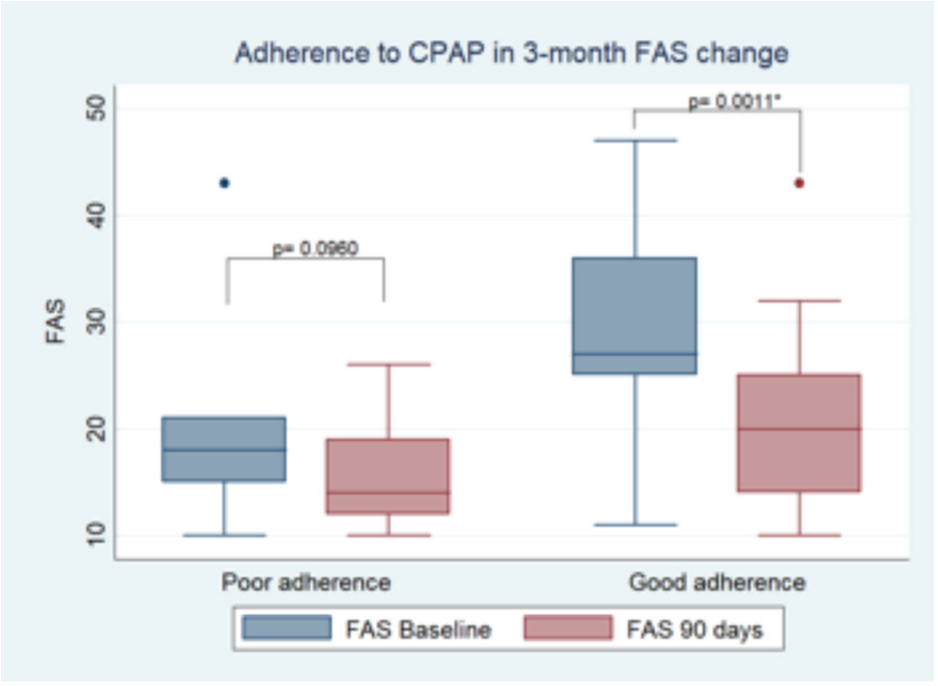

Fig. 4. Adherence to CPAP impact in FAS change at 3-month. FAS: Fatigue Assessment Scale. Compliance to CPAP therapy was evaluated by reading SD card at 3-month. Good compliance was defined as "device use for more than 4 hours per night and at least 70% of total number of nights".
*Statistical significance using paired T-test

3.5-9.1; p = 0.0011) while poor compliance to CPAP therapy missed the statistical significance (4.4, 95% CI -1.0-9.9; p = 0.0960). Similarly, a statistical significative reduction in ESS score at 3-month was also demonstrated only in good compliance (2.92, 95% CI 1.1-4.7; p = 0.0041) when compared to poor one (3.14, 95% CI -0.1-6.3; p = 0.0519).

Discussion

The analysis of the cohort from our institution demonstrate that OSA affects the majority of patients with sarcoidosis in our center and it must be taken into account during the clinical evaluation. The impressively high OSA prevalence might be explained by an impaired upper airway stability. We found that BMI, lower lung volumes in pulmonary function tests (TLC) and parenchymal involvement (Scadding stage) are independent predictors of OSA in sarcoidosis. Thus, the caudal traction on the upper airways results in increased collapsibility during the sleep due to the deposition of fat around upper airways and the reduction of the lung volumes. Moreover, advanced Scadding stages (II-to-IV) are independent predictors of higher AHI. The design of the study is not suitable to investigate if such significant association resulted from the inflammation mediators of the disease's activity or the concurrent steroid treatment. Considering that no patient received any other second-line treatment for sarcoidosis, the adjusted multivariate analysis of the AHI did not provide us with robust data to support the hypothesis of steroids as a possible risk factor or *primum movens* of sleep disorder because of the weight gain and BMI impact during treatment time. Notably, the small sample size and the limits might affect such investigations and we think that a call for further studies focusing on the relationship between steroids and OSA is justified.

Despite the high prevalence of OSA in patients affected by sarcoidosis, as far as we are aware, no data is available regarding the effect of OSA treatment with CPAP.

In this study, we report for the first time that CPAP treatment has a positive impact on reducing fatigue and sleepiness in sarcoidosis. Patients tolerant to positive pressure at the 3-month goal for adherence assessment, did show that a good compliance can reduce fatigue and sleepiness. These results are particularly encouraging because no exhaustive treatment demonstrate d efficacy for fatigue in sarcoidosis. Thus, the investigation and the treatment of comorbidities such as OSA, might represent a first step for treatment of fatigue status in sarcoidosis. Moreover, CPAP therapy improved symptoms of sleepiness assessed with ESS questionnaire more than the minimal clinically important difference at 3-month. Considering that the definition of excessive daytime sleepiness was met at baseline only in a small proportion, we may agree the clinical value of such ESS reduction is slightly limited. Though, we investigated the effect of positive pressure on sleepiness assessed with ESS score not only because no previous data was available in literature but also with regard to future, controlled studies specifically designed to address the role of CPAP treatment in sarcoidosis. Ultimately, a significant drop-out rate or poor adherence should be taken into account in forthcoming studies with CPAP treatment and face to face appointments or wireless telemonitoring could be possible, feasible strategies in order to improve CPAP compliance.

Limitations

The study demonstrated limitations. We performed a single-center study and the described prevalence of OSA may suffer from a selection bias that only a further, multi-center investigation may solve in order to generalize that Sleep Apnea is highly prevalent in sarcoidosis. A selection bias could also be implied in the higher FAS score at baseline in none-to-mild subjects when compared to the FAS score of moderate-to-severe cohort: FAS correlates with gender and the great proportion of females in none-to-mild cohort did play a role, resulting in the overestimation of the FAS. Also, the overnight sleep study was performed using a portable device for diagnosis of OSA instead of supervised in-laboratory polysomnography. In order to limit the possible overestimations[21], one polysomnologist performed a manual editing of the total recording time of the whole sleep studies. We chose a single arm design without any control group when assessing the CPAP treatment effect on fatigue. Thus, the results must be considered as explorative findings and the effect of CPAP on fatigue raises a clinical question that should be addressed in future studies.

Conclusions

Obstructive Sleep Apnea Syndrome is prevalent in the Sarcoidosis Clinic of our institution and has a great impact on fatigue status in patients affected by sarcoidosis. A higher upper airway collapsibility could be implied in such important prevalence of OSA in sarcoidosis due to the lower lung volumes and excessive BMI. Advanced Scadding Stages with severe parenchymal involvment is also an independent predictor of AHI and forthcoming studies should investigate on the association between steroids and OSA in sarcoidosis. Treatment with CPAP successfully reduced fatigue and daytime sleepiness symptoms after three months of therapy in those with good adherence to positive pressure treatment.

Contributions

Drs Mari PV, Pasciuto G and Richeldi L had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the statistical analysis. We also acknowledge the patient's society "Amici Contro La Sarcoidosi Italia ONLUS" for the invaluable support. Concept and design: PVM, GP, LR, GMC, MS. Acquisition and collection of data: PVM, MS, JS, FB. Data analysis: PVM, LR, GMC. Manuscript drafting: PVM, LR, GP, GMC. Final approval of the manuscript: all authors.

Disclosure Statement

The design, management, analysis and reporting of the study are independent. We did not receive any funding.

Abbreviations: AHI, Apnea-Hypopnea Index; BMI, Body Mass Index; CPAP, Continuous Positive Airway Pressure; CS, Corticosteroids; DLCO/Va, Diffusing Capacity divided by the Alveolar Volume; ESS, Epworth Sleepiness Scale; FAS, Fatigue Assessment Scale; FVC, Forced Vital Capacity; MID, Minimum Important Difference; ODI, Oxygen Desaturation Index; OSA, Obstructive Sleep Apnea; SDB, Sleep-Disordered Breathing; TLC, Total Lung Capacity

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2); 179-183 DOI: 10.36141/svdld.v37i2.8181

A unique case of ovarian manifestation of systemic vasculitis that mimics ovarian cancer

Ada Bielejewska[1], Arkadiusz Bociek[1], Martyna Bociek[2], Andrzej Jaroszyński[3]

[1] Collegium Medicum, Jan Kochanowski University in Kielce, Poland, Jan Kochanowski University in Kielce, Poland; [2] Faculty of Medical Science, Higher School of Economy, Law and Medical Science of professor Edward Lipiński in Kielce, Poland; [3] Department of Nephrology, Institute of Medical Science, Jan Kochanowski University in Kielce, Poland

Abstract. *Heading objectives:* Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) that may involve any organ. Rarely, clinical manifestation of inflammatory changes may resemble tumours, which, combined with untypical ovarian localization, may cause misdiagnosis and treatment delay. *Case report:* In this paper, we present the case of ovarian tumour-like lesion being the first manifestation of GPA and mimicking ovarian cancer. *Conclusion:* In case of a patient presenting with a tumour of untypical features, differential diagnosis should include inflammatory processes, including vasculitis. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 179-183)*

Key words: granulomatosis with polyangiitis, ovarian cancer, systemic vasculitis, Wegener's granulomatosis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are a group of necrotizing systemic autoimmune diseases, affecting small- and medium-sized blood vessels, such as capillaries, arterioles and venules. As immune complex deposits within the inflammatory changes are scarce (or even absent), the process is commonly described as pauci-immune vasculitis. A number of predisposing factors (for example genetic or environmental factors, infections, drugs) can cause the production of autoantibodies active against myeloperoxidase (MPO-ANCAs) or proteinase 3 (PR3-ANCAs), both present in azurophilic granules of neutrophils. When neutrophils primed by proinflammatory cytokines are activated by interacting with ANCA, they tend to accumulate within the walls of the vessel, causing a number of inflammatory processes ended with the death of the cell, which causes injury of the surrounding tissue. Coagulation factors and serum proteins drawn to the injured epithelium cause fibrinoid necrosis (1).

AAV may involve any organ, such as the lungs, kidneys, gastrointestinal tract, brain, heart, skin, eyes, pancreas, liver, testicles or ovaries (1–5). Due to its many possible localizations and its pathogenesis, there's a vast variety of signs and symptoms that may occur – from non-specific symptoms of inflammation (fever, weight loss, fatigue, anaemia), local organic damages (for example rashes, petechiae, purpura) to multi-organ involvement of often rapidly progressing course. The ACR/EULAR (American College of Rheumathology/ European League Against Rheumathism) 2017 provisional classification criteria for GPA include bloody nasal discharge, ulcers, crusting or sinonasal congestion, nasal polyps, hearing loss or reduction, cartilaginous involvement, red or painful eyes, C-ANCA or PR3-ANCA, eosinophilia, nodule, mass or cavitation on chest im-

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Correspondence: Arkadiusz Bociek
Collegium Medicum, Jan Kochanowski University in Kielce, Poland, Jan Kochanowski University in Kielce, Poland
E-mail: arkadiusz33333@gmail.com

aging and granuloma on biopsy (6). Typical findings include upper respiratory tract involvement and often renal disorder (1,4,7). Rarely, clinical manifestation of inflammatory changes may resemble tumours, which, combined with an untypical localization (for example within the reproductive system), can cause misdiagnosis and improper treatment (4).

Case Presentation

A 48-year-old woman was hospitalized due to severe pain in the lumbosacral region, hydronephrosis of the left kidney with dilation of the left ureter (abdominal part) caused by outside infiltration (CT and MRI were performed). During her stay at the urology ward, she had fever, increased CRP (C-reactive protein) (161 mg/l) and PCT (procalcitonin) (0,1 ug/ml). Both urine and blood culture examination were carried out and the results came back negative four times. Despite that, owing to the high CRP level, she was empirically treated with antibiotics, without any outcome. Blood pressure was normal. Renal parameters were gradually increasing but the function of the kidneys was preserved. The patient underwent gastroscopy, colonoscopy and non-contrast abdominal CT and some fluid in pleural, pericardial and abdominal cavity were found. Moreover, the CT revealed a large tumour (dimensions 34x27x51 mm with 5 mm calcification) possibly infiltrating the left internal obturator and iliopsoas muscle (as showed in Figure 1). The size and location of the tumour, together with ROMA (the Risk of Ovarian Malignancy Algorithm, using CA125 and HE4 concentration in patient's serum) score of 96,7%, raised the suspicion of disseminated ovarian cancer and inclined the need for gynaecological consultation. Small erythrocyturia revealed in urinalysis was firstly associated with cancerous infiltration of the urinary tract.

Nephrostomy of the left kidney was performed with no urine outflow. Due to the lack of diuresis, primary renal diseases, rather than obstruction of the ureter, were investigated and, after a nephrological consultation, additional laboratory tests, such as MPO-ANCA and PR3-ANCA, were carried out. Due to acute kidney injury (increasing renal parameters: creatinine 5,99 mg/dl, urea 87 mg/dl), the patient was transferred to the Nephrology Clinic, where a haemodialysis catheter was placed. After haemodialysis, patient's general state improved but

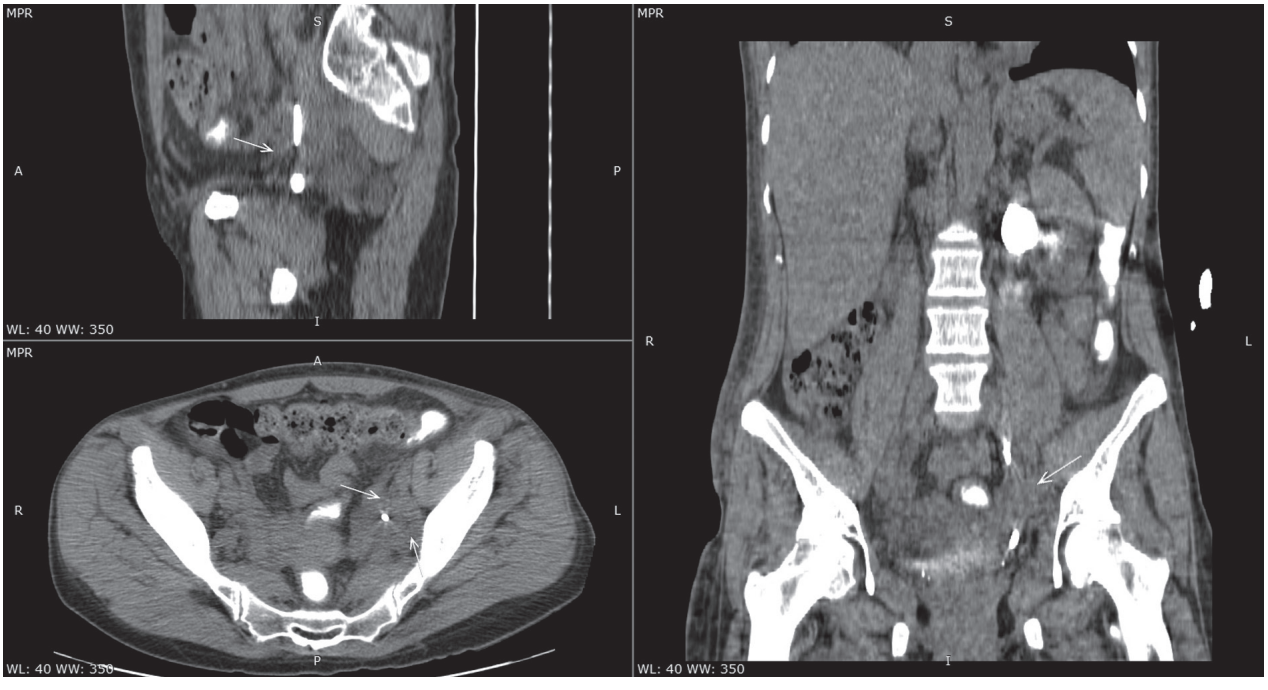

Fig. 1. CT multiplanar reconstruction showing a tumour (34x27x51 mm with 5 mm calcification) suspected of being an ovarian cancer. The arrows point out the lesion

kidney function wasn't retrieved. Meanwhile, the patient underwent diagnostic laparoscopy with removal of left uterine appendages. Due to the size of the tumour, it came as a surprise that the peritoneum was intact and with no signs of infiltration.

The results of the laboratory tests came back three days after the surgery and both MPO and PR3-ANCA were found (32 IU/ml and> 200 IU/ml respectively), giving the diagnosis of vasculitis, suggesting GPA. Histopathological examination revealed the involvement of small vessels with necrotizing and granulomatous inflammatory infiltrate predominantly composed of neutrophils as well as lymphocytes and eosinophils and chronic purulent inflammation of the connective tissue surrounding iliac arteries and left ureter, inflammatory tumour of the left ovary with no sign on neoplasm within the uterine appendages, which confirmed the diagnosis of GPA.

Later, the patient complained of recurrent nasal bleeding and laryngological consultation was made. Nasal ulcer was found and then biopsy was performed. Histopathological examination's result, combined with clinical symptoms revealed the progression of GPA. The patient was treated with 100mg/d oral cyclophosphamide and 3 x 1.0 g intravenous methylprednisone, followed by 40 mg/d oral prednisone. Due to hepatitis B in the past and unknown current level of viral DNA in serum, the patient was disqualified from rituximab treatment. Despite general state's improvement, renal function wasn't retrieved. The patient was haemodialyzed 3 times a week and treated with immunosuppressive drugs as above.

The patient was re-hospitalised due to anaemia (4,3 g/dl), haemoptysis and purpura on both lower legs. CT revealed diffuse alveolar haemorrhage (figures 2 and 3). She was given a high dose of cyclophosphamide and overwent seven plasmapheresis complicated by transient leukopenia treated with granulocyte colony stimulating agent (G-CSF). After the treatment, the patient was discharged from hospital in general good condition. After a year of haemodialysis, the patient successfully underwent a kidney transplant.

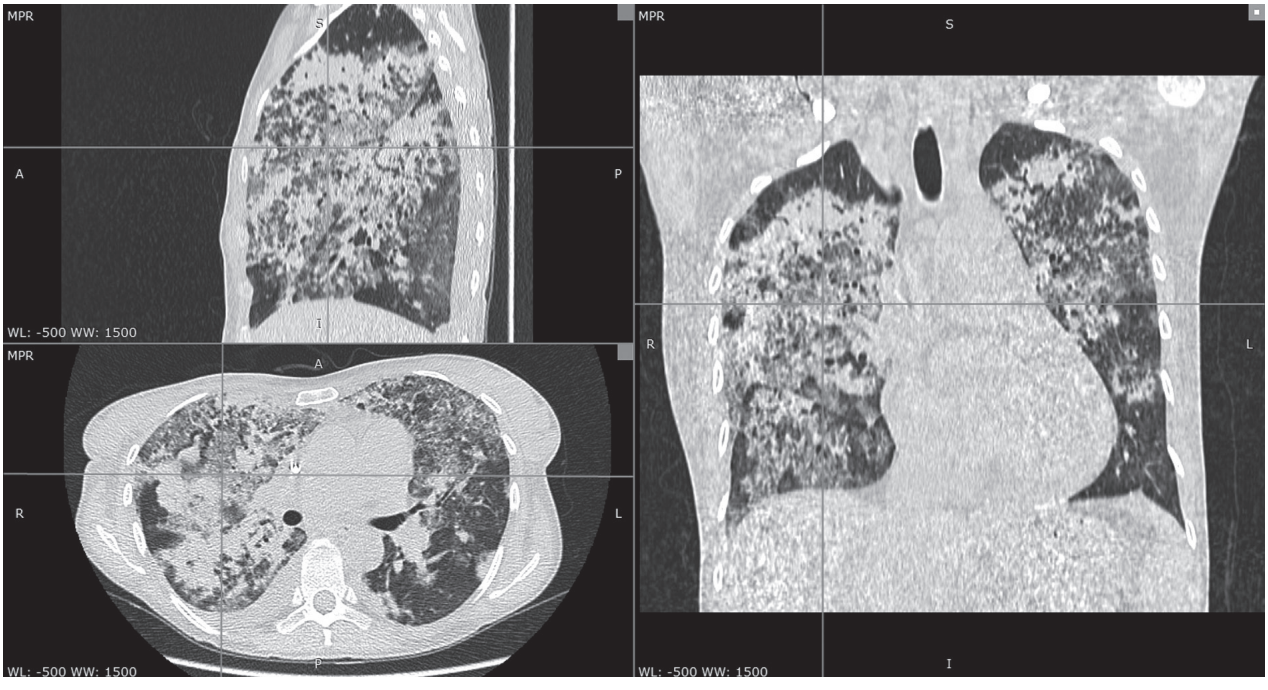

Fig. 2. CT multiplanar reconstruction showing diffuse alveolar haemorrhage in course of granulomatosis with polyangiitis.

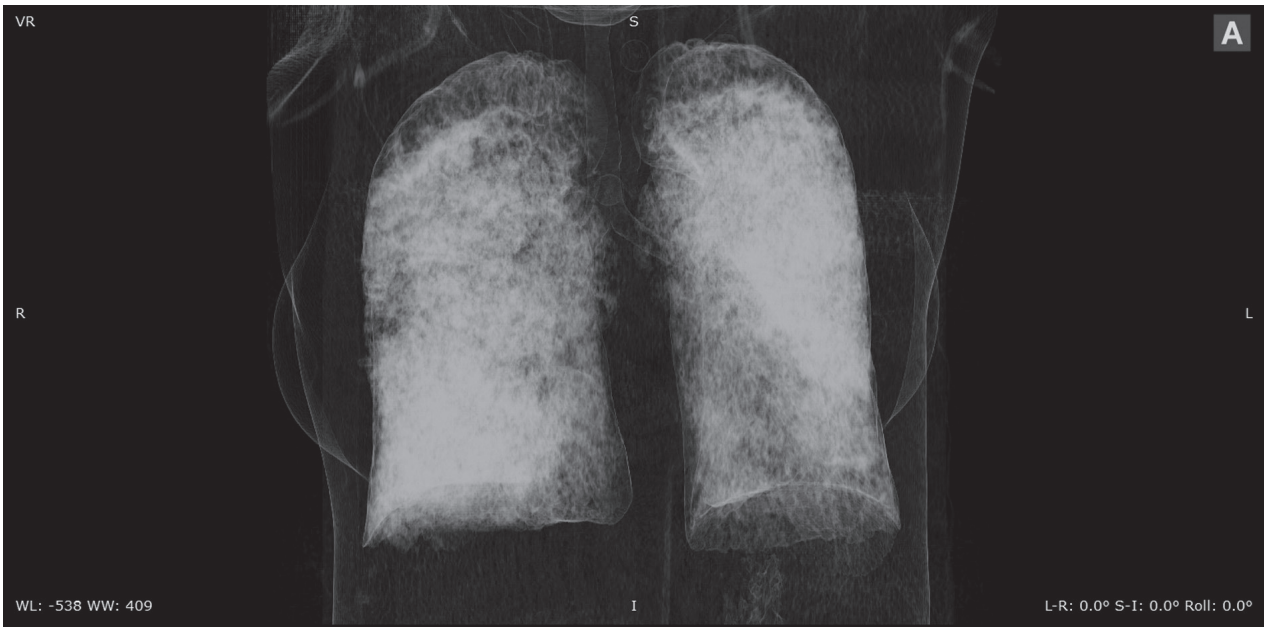

Fig. 3. Virtual reality 3D reconstruction from CT scan (presented on figure 2) showing diffuse alveolar haemorrhage in course of granulomatosis with polyangiitis

Discussion

To our best knowledge, no case of GPA with ovarian manifestation as a first symptom has ever been described. On admission, our patient presented with urinary retention and hydronephrosis with preserved renal function. Except for inflammation, there were no systemic signs. Moreover, hypertension, pulmonary changes or other symptoms that could point towards GPA were absent, which additionally delayed the diagnosis. Due to the tumour in the true pelvis, suspected to be a disseminated ovarian cancer (high ROMA, infiltration of the left ureter, muscles and vessels), as well as the lack of response to the antibiotics, the decision was made to operate and perform an intra-operative biopsy. The decrease in renal function, as well as the appearance of respiratory tract symptoms showed only after the resection was performed and thus began the diagnosis of AAV. Positive results of MPO-ANCA and PR3-ANCA, combined with the biopsy results (inflammatory tumour), confirmed the diagnosis of GPA.

Some cases of tumour-like lesions in the female reproductive system were reported in the course of other types of systemic vasculitis: polyarteritis nodosa, giant cell arteritis, EGPA (eosinophilic granulomatosis with polyangiitis) and Takayasu arteritis. (2,4,8–10). In the course of GPA, lesions were observed in other organs but not in the ovary (4). Due to a high suspicion of malignancy, surgical treatment was also adopted but histopathological examination revealed vasculitis with no signs of malignancy in these cases.

Even though the ovary seems to be an extremely rare localisation of an inflammatory process in vasculitis, it is important to remember about it in differential diagnosis of an ovarian cancer, especially in cases of untypical course. In patients diagnosed with vasculitis (especially AAV with systemic symptoms), there is a high probability that observed lesions are non-malignant so in these cases investigation should be more insightful than usual due to a possibility of avoidance of unnecessary operation.

In case of a patient suffering from AAV and presenting with a tumour of rare localisation or untypical radiological features, differential diagnosis of cancer should also include inflammatory tumours. In such a case, the decision of further management, especially an operation, should be taken with caution, as sometimes biopsy of the affected organ could be considered. On the other hand, if the recognition of vasculitis is questionable or the disease gives symptoms in an isolated location, the risk of the cancer progression may be too high to postpone necessary

treatment (resection of the lesion). Thus, treatment should be adjusted to the patient very carefully and both overall risk and patient's quality of life have to be considered.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2); 184-191 DOI: 10.36141/svdld.v37i2.9150

Long-term outcomes of epoprostenol therapy in sarcoid associated pulmonary hypertension

Eric Abston[1], Matthew Moll[2], Stephanie Hon[1], Praveen Govender[1], Jeffrey Berman[3], Harrison Farber[4]
[1]Boston University Medical Center; [2]Brigham and Womens Hospital; [3]Boston University Medical Center; [4]Tufts Medical Center

Abstract. Sarcoidosis-Associated Pulmonary Hypertension (SAPH) is a common finding in patients with chronic sarcoidosis and is associated with increased mortality. The optimal treatment for SAPH is not known; however, therapies approved for Group 1 pulmonary hypertension have improved hemodynamics and functional status. Prostanoids, including epoprostenol, have been therapeutic in short-term studies of SAPH, but long-term efficacy is unknown. In this study, we evaluated the long-term effect of epoprostenol therapy in 12 patients with SAPH. Hemodynamic assessment after an average of 4.1 years of epoprostenol therapy demonstrated significant improvement in mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output; furthermore, patients demonstrated improved NYHA functional class. To evaluate further the long-term effect of epoprostenol, we compared survival of SAPH patients to a cohort of hemodynamically matched patients from the same center treated with epoprostenol for Idiopathic Pulmonary Arterial Hypertension (IPAH). Interestingly, there was no difference in survival, despite the additional systemic disease burden of the SAPH subjects. Subgroup analysis by Scadding stage demonstrated that Scadding stages 1-3 had improved survival compared to Scadding stage 4. These observations suggest that epoprostenol is an effective long-term therapy for patients with SAPH; it improves hemodynamics, functional class, and provides survival similar to that seen in a hemodynamically-matched cohort of IPAH patients. Furthermore, we identify a subgroup of SAPH patients (nonfibrotic lung disease Scadding 1-3) who may derive significant benefit from prostanoid therapy. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 184-191)*

Key Words: Sarcoid associated pulmonary hypertension, epoprostenol, sarcoidosis, pulmonary hypertension.

Introduction

Sarcoidosis-Associated Pulmonary Hypertension (SAPH) is a complication of sarcoidosis; however, the exact incidence is unknown. Using echocardiography, the largest studies have reported pulmonary hypertension (PH) in 5-50% of patients with known sarcoidosis[1, 2, 3]. Other series using right heart catheterization, have reported pulmonary hypertension in 49-73% of patients with symptomatic sarcoidosis[4, 5]. However, determining the exact prevalence of SAPH in patients with sarcoidosis is difficult because of the heterogeneity of the population and the varying severity of the underlying sarcoidosis. Yet, it is clear that the presence of SAPH confers a poor prognosis compared to sarcoidosis without SAPH[2, 6, 7]. SAPH occurs due to complex interactions between sarcoid involvement in the lung parenchyma and the pulmonary vasculature. Several distinct mechanisms have been suggested by which sarcoidosis can induce pulmonary hypertension, including: hypoxia, pulmonary artery vasculitis, sarcoidosis-associated heart failure, fibrotic destruction of pulmonary vasculature, occlusion of pulmonary vasculature by enlarged

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Correspondence: Eric Abston
Pulmonary Center
715 Albany St
Boston, MA 02118

lymph nodes or granulomatous tissue, thromboembolic disease and sarcoidosis-induced hepatic disease and subsequent portopulmonary hypertension[8]. Moreover, in an individual patient, several of these mechanisms may occur simultaneously and contribute to the development of SAPH[9].

Treatment of SAPH has focused separately on optimization of the treatment of the underlying sarcoidosis and management of the PH as distinct issues. Studies specifically evaluating the effect of treating sarcoidosis with immunomodulatory therapy alone have demonstrated mixed results on pulmonary hemodynamics[7, 10, 11, 12]. SAPH is classified as WHO Group 5 PH in part because of the multiple disease processes which affect the lung in SAPH, and because similar diseases produce PH that does not respond well to vasodilator therapy.

In idiopathic pulmonary arterial hypertension (IPAH), intravenous prostanoid therapy improves functional and clinical status, as well as survival[13]. Likewise, in patients with SAPH, prostanoids have been shown to be effective vasodilators, whether administered as inhaled or intravenous therapy[14, 15, 16, 17, 18]. Trials evaluating the effect of endothelium receptor antagonists (bosentan and ambrisentan) and phosphodiesterase-5 inhibitors (sildenafil and tadalafil) have also demonstrated improved hemodynamics in some patients with SAPH[19, 20, 21]. Previously, short-term benefits of epoprostenol in a small series of patients with SAPH[16] have been demonstrated. However, there exist limited data regarding long-term outcomes of SAPH patients treated with epoprostenol.

In this retrospective cohort study, we report the largest group of patients with SAPH treated with epoprostenol. Furthermore, the observation period is greater than previously published cohorts. In addition, we characterize this patient population in order to better understand the long term effects of epoprostanol therapy in patients with SAPH. Also, unlike previous studies, we compared the response in this cohort of SAPH patients to a hemodynamically-matched cohort of IPAH patients treated with epoprostenol at the same institution. Finally, we compared survival between fibrotic (Scadding stage 4) and nonfibrotic (Scadding stage 1-3) subgroups of pulmonary sarcoidosis in SAPH to assess whether the presence of fibrotic lung disease affects survival.

Methods

Design and data collection

We conducted a retrospective review of all patients treated with epoprostenol from January 2000 to January 2018 in accordance with a protocol approved by the University Institutional Review Board. Inclusion criteria were PH patients treated with intravenous epoprostenol with the diagnosis of sarcoidosis or IPAH. The diagnosis was based on review of the medical record, including compatible historical information and/or pathology findings. All patients were diagnosed with SAPH by appropriate hemodynamic parameters at right heart catheterization (RHC; see Table 1). Patients were excluded if there was evidence of any of the following: connective tissue disease, portal hypertension, cardiac disease, HIV disease, history of anorexigen or illicit drug use, or thromboembolic disease. For each case, we collected patient demographics, stage of sarcoidosis, treatment of sarcoidosis, pulmonary function testing, echocardiography, baseline and post-treatment hemodynamics, and long-term clinical outcome.

Vasodilator Treatment with Epoprostenol

Long-term IV epoprostenol therapy was administered via a centrally inserted tunneled catheter. Dose adjustments were made as dictated by patient symptoms and clinical status. Patients were treated with supplemental oxygen as required to maintain oxygen saturation $\geq$ 90%. Patients underwent surveillance RHC to assess their response to treatment as dictated by symptoms and clinical status.

Immunosuppressive therapy for sarcoidosis

Corticosteroid or immunosuppressive therapy was initiated or continued based on standard indications for treatment of sarcoidosis (ie, hypercalcemia, pulmonary, ocular, or CNS involvement)[22].

Statistical analyses

Student's T-test in Microsoft Excel was used for inter-group comparisons. A paired T-test was used for intra-group comparisons. Means and standard deviations are reported. Time-to-death between SAPH and IPAH groups, as well as subgroup

Table 1. Baseline patient characteristics. Demographics, promonary function testing, and echocardiography data obtained at diagnosis. Epoprostenol dose at initiation was 10 ± 3 ng/kg/min and titrated up as tolerated to an average dose of 64 ± 48. New York Heart Association Functional Class improved from 3.5 ± 0.5 at initiation of epoprostenol to 2.6 ± 0.8 p = 0.005.

	Demographics		
Sex (Male)	4 (33%)		
Age (Years)	48 ± 10		
BMI	29 ± 9.5		
Smoker	6 (50%)	2/6 active smokers	
Race			
AA	8 (67%)		
Caucasian	3 (25%)		
Hispanic	1 (8%)		
Pulmonary Function Testing	Liters	% Predicted	
FVC	1.93 ± 0.5	60 ± 16	
FEV1	1.3 ± 0.4	54 ± 14	
FEV1/FVC	68 ± 12		
TLC	3.3 ± 0.6	62 ± 12	
DLCO (mL/mmHg/min)	6.6 ± 3.7	32 ± 17	
Echocardiogram			
EF %	57 ± 12		
PASP mmHg	69 ± 17		
RV Dilation:			
Severe	6 (50%)		
Moderate	3 (25%)		
Mild	1 (8%)		
None	2 (17%)		
	Initiation	Maintenance	P-Value
Epoprostenol Dose ng/kg/min	10 ± 3	64 ± 48	0.002
NYHA FC	3.5 ± 0.5	2.6 ± 0.8	0.005

analysis between SAPH pooled as Scadding stages 1-3 and Scadding stage 4 subgroups was compared using a log-rank test with R software (R Development Core Team, 2008). Time-to-death analysis was performed only in patients treated with epoprostenol for ≥ 30 days. In the survival analysis, transplant was considered the same as death.

Results

Twelve patients with SAPH fulfilling the study criteria were identified after screening all patients treated with epoprostenol during the defined time frame and included in these analyses. (Table 1). 4 (33%) were male, 6 (50%) were smokers (2/6 active smokers), and 7 (67%) were African American. Average age was 48 ± 10 years and average BMI was 29 ± 9.5. At baseline, the FVC was 1.93 ± 0.5 L (60 ± 16% predicted), FEV1 1.3 ± 0.4 L (54 ± 14% predicted), and FEV1/FVC 68 ± 12. TLC was 3.3 ± 0.6 L (62 ± 12% predicted) and DLCO 6.6 ± 3.7 mL/mmHg/min (32 ± 17% predicted).

The diagnosis of sarcoidosis was established in 67% of subjects by clinical findings and a biopsy specimen demonstrating non-necrotizing granulomas (Table 2). In the other 33% of subjects, sarcoidosis was diagnosed by typical clinical features in the absence of biopsy. 58% of subjects had a

Table 2. Description of sarcoidosis features. Eight of twelve patients had biopsy proven sarcoidosis. Seven of Twelve patients had Scadding class 4 sarcoidosis. Extrapulmonary organ involvement and sarcoidosis medications are listed.

Sarcoid Features:	
Diagnosis	
Biopsy	8 (67%)
Clinical	4 (33%)
Sarcoid Stage	
1-3	5 (42%)
4	7 (58%)
Extrapulmonary Organ Involvement	
Ocular	3 (25%)
CNS	3 (25%)
Bone Marrow	1 (8%)
Treatment	
Prednisone	6 (50%)
Hydroxychloroquine	2 (16%)
Methotrexate	2 (16%)
Azathioprine	1 (8%)
Lung Transplant	2 (16%)

Scadding stage of 4, the remaining 42% were classified in stages 1-3. All subjects had pulmonary involvement. Frequency of extrapulmonary organ involvement was: CNS 2 (25%), ocular 2 (25%), bone marrow 1 (8%). At initiation of epoprostenol therapy, 6 (50%) of patients were receiving prednisone, 2 (16%) plaquenil, 1 (16%) methotrexate, 1 (8%) azathioprine, and 1 (8%) infliximab (1 8%); 2 (16%) of the subjects ultimately underwent lung transplantation.

By transthoracic echocardiogram, LVEF was estimated at 57 ± 12% and PASP 69 ± 17 mm Hg (Table 1). Right ventricular (RV) dilation was assessed as severe in 6 (50%), moderate in 3 (24%), and mild in 1 (8%). In the remaining 2 (16%), RV size was normal. Hemodynamic measurements from the diagnostic RHC are shown in Table 3: mPAP was 57 ± 8 mmHg, PVR 12.4 ± 2.8 WU, CO 3.7 ± 0.8 L/min (Thermodilution, TD), and CI 2.0 ± 0.4 L/min/m^2. Initiation of epoprostenol was guided by invasive hemodynamic monitoring and side effects; at discharge (after initial titration), the dose was 10 ± 3 ng/kg/min. Acute hemodynamic changes with initiation of epoprostenol have been previously reported[16]; as in that study, we observed significant improvements in CO (4.1 ± 0.7 L/min pre, 6.2 ± 1.4 L/min post TD, p = 0.005) and PVR (11.8 ± 2.8 pre, 6.3 ± 2.9 WU post units, p = 0.008).

Table 3. Diagnostic Right Heart Catheterization (N = 12)

Diagnostic RHC	
RV sys (mmHg)	87 ± 15
RA dia (mmHg)	14 ± 5.2
PAP sys (mmHg)	88 ± 13
PAP dia (mmHg)	39 ± 8
mPAP (mmHg)	57 ± 8
PCWP (mmHg)	13 ± 5
CO TD (L/min)	3.7 ± 0.8
CI TD (L/min/m^2)	2 ± 0.4
BSA (m^2)	2 ± 0.3
PVR TD (WU)	12.4 ± 2.8
SVR TD (mmHg min mL^{-1})	1922 ± 477

Hemodynamic measurements obtained to diagnose pulmonary hypertension.
RV (Right ventricle), PAP (Pulmonary Arterial Pressure), mPAP (Mean Pulmonary Arterial Pressure), PCWP (Pulmonary Cappillary Wedge Pressure), CO TD (Cardiac Output via thermodilution method), CI Cardiac Index), BSA (Body Surface Area), PVR (Pulmonary Vascular Resistance), SVR (Systemic Vascular Resistance).

After discharge, all patients were followed by regular clinic visits and surveillance RHC as clinically indicated. At initiation of epoprostenol, some patients developed expected manageable prostanoid-related side effects; which resolved with treatment and/or time. Several patients developed transient minor V/Q mismatch, treated conservatively, that resolved within 4-6 weeks. No patients had persistent V/Q mismatch or shunting.

The epoprostenol dose was titrated to symptoms and clinical status. Patients underwent surveillance RHC (Table 4) at a mean duration of 4.1 years after initiation of epoprostenol; at that time, mean epoprostenol dose was 64 ± 48 ng/kg/min. In addition to epoprostenol, some patients were also treated with tadalafil (4 patients; 33%), sildenafil (1 patient; 8%), and ambrisentan (1 patient; 8%). Long-term epoprostenol therapy was associated with a significant improvement in hemodynamics (Table 4): mPAP (Pre 59 ± 10 vs Post 36 ± 11 mmHg, p = 0.002), PVR (Pre 11.8 ± 2.0 vs Post 4.3 ± 1.9 WU < 0.001) and CO (Pre 4.0 ± 0.7 vs Post 5.8 ± 1.5 L/min, p = 0.002) CI (Pre 2 ± 0.3 vs Post 3 ± 0.6 L/min/m^2, p = 0.008). NYHA-FC had improved on average one full classification, 3.5 ± 0.5 pre-treatment to 2.6 ± 0.8 post-treatment (0.005).

Survival of patients with SAPH treated with epoprostenol was compared to patients with hemodynamically-similar IPAH treated with epoprostenol (Table 5). At initiation of epoprostenol therapy, there

Table 4. Surveillance Right Heart Catheterizations

	Diagnostic	Follow up	p Value
RV systolic (mmHg)	88 ± 22	51 ± 23	0.015
RV diastolic (mmHg)	13 ± 4.6	2.8 ± 3.7	0.002
PAP systolic (mmHg)	90 ± 18	53 ± 23	0.006
PAP diastolic (mmHg)	40 ± 10	24 ± 7	0.006
mPAP (mmHg)	59 ± 10	36 ± 11	0.002
PCWP (mmHg)	12 ± 3	11 ± 4	0.46
CO TD (L/min)	4.0 ± 0.7	5.8 ± 1.5	0.01
CI TD (L/min/m^2)	2 ± 0.3	3 ± 0.6	0.008
BSA (m^2)	1.9 ± 0.2	1.8 ± 0.2	0.43
PVR TD (WU)	11.8 ± 2.1	4.3 ± 1.9	< 0.001
SVR TD (mmHg min mL^{-1})	1652 ± 381	1347 ± 512	0.19

Surveillance RHC, with mean follow up of 4.1 years, showing improvement in hemodynamics compared to pre-treatment diagnostic catheterization. N = 7 patients. See Table 3 Legend for abbreviations.

Table 5. Comparison between SAPH and IPAH patients

	IPAH (N = 52)	SAPH (N = 12)	P Value
Age (Years)	57 ± 16	48 ± 10	0.07
Sex (% Male)	38	33	0.75
mPAP (mmHg)	56 ± 13	57 ± 8	0.88
PVR (WU)	12.2 ± 3.9	12.4 ± 2.8	0.89

IPAH and SAPH subjects are similar in demographics and disease severity.

was no significant difference between SAPH and IPAH groups with respect to age 48 ± 10 vs 57 ± 16 years (p = 0.07) or sex 33 vs 38% male (p = 0.75). Diagnostic hemodynamic measurements were also similar between SAPH and IAPH groups: mPAP 57 ± 8 vs 56 ± 13 mmHg (p = 0.88), PVR 12.4 ± 2.8 vs 12.2 ± 3.9 WU (p = 0.89). Mean survival for the IPAH patients was 43 ± 41 months and 54 ± 57 months for the SAPH patients (Figure 1A). Time-to-death

Figure 1A:

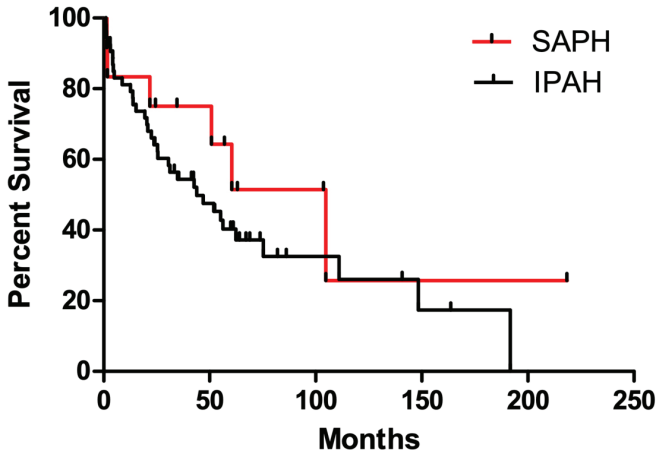

Figure 1B:

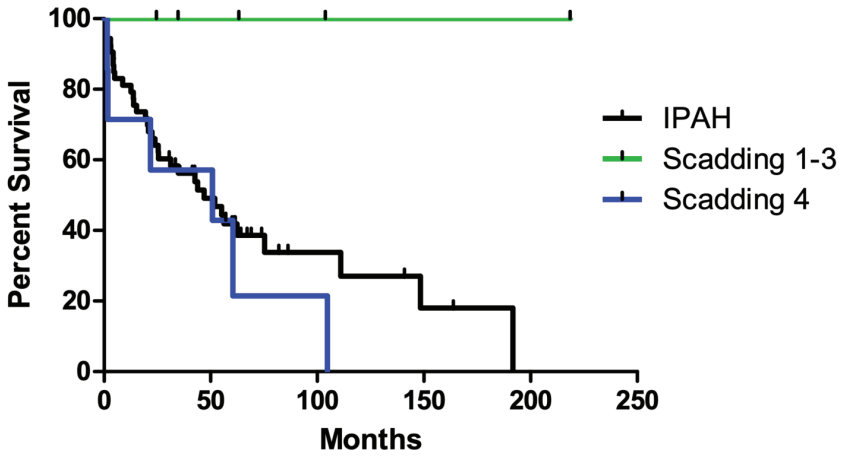

Fig. 1a. Log-rank test comparing survival of patients with SAPH vs IPAH. There is no difference in time-to-death between SAPH and IPAH. (Mean survival in months SAPH 62 ± 60 vs IPAH 46 ± 42, p = 0.28). **Fig. 1b.** Survival of SAPH Scadding stages 1-3 (non-fibrotic disease) is significantly greater than SAPH Scadding stage 4 (fibrotic disease) by log-rank test (Scadding stages 1-3 89 ± 79 months vs Scadding stage 4 42 ± 37 months p = 0.017). Survival of SAPH Scadding stages1-3 is also significantly greater than IPAH p = 0.02. There was no difference in survival between Scadding 4 and IPAH p = 0.43.

analysis of these cohorts demonstrated that there was no difference in survival of SAPH patients compared to IPAH patients by log rank test (p = 0.28).

Analysis of the SAPH cohort by Scadding classification (Figure 1B) Scadding stages 1-3 (nonfibrotic disease) vs Scadding stage 4 (fibrotic disease) revealed significantly longer survival in the Scadding stage 1-3 group (mean 89 ± 79 months) vs the Scadding stage 4 group (42 ± 37 months), (p = 0.02). No deaths were observed in the Scadding stages 1-3 group, whereas five deaths occurred in the Scadding stage 4 group. Comparison of SAPH Scadding stages 1-3 vs IPAH demonstrated that SAPH Scadding stages 1-3 had significantly higher survival over the follow up period (p = 0.02). Then SAPH Scadding stage 4 group survival was compared separately with that of IPAH; there was no difference (p = 0.43).

Discussion

We have described a cohort of patients with SAPH treated long-term with epoprostenol. This study confirms the hemodynamic response to epoprostenol previously observed in SAPH patients[16]. All patients in this cohort demonstrated both improved hemodynamic and functional status. Of note, this is the largest cohort of SAPH patients treated with epoprostenol to date and builds on the findings previously reported by Fisher, et al[16]. In addition, this is the first study to compare survival between patients with SAPH and IPAH treated with epoprostenol, and compare survival with epoprostenol therapy by Scadding stage.

SAPH occurs via multiple pathological processes, any, or all of which, might affect a given individual. Thus, difference in outcome observed in small patient cohorts are likely due to heterogeneity of SAPH and the predominance of various pathways in the progression of the disease. That said, it is clear that survival in patients with SAPH is significantly less than in patients with sarcoidosis alone. In one study, five-year survival in patients with SAPH was 55%[10]. Similarly, the five-year survival of our cohort was 42%. Importantly, two of our patients have been treated with epoprostenol for greater than 17 years. Such survival suggests that prostanoid therapy can be highly effective long-term therapy for SAPH.

This study also confirms previous reports that the presence of pulmonary fibrosis confers a negative prognosis. In this cohort, there was no difference in the baseline hemodynamics of fibrotic and nonfibrotic patients; and, there was no difference in hemodynamic response to epoprostenol therapy by Scadding class. Although both groups experienced a similar improvement in functional class, there was a marked difference in survival with no mortality in the nonfibrotic subgroup. Dobarro previously described a survival difference between Scadding stages 1-3 and stage 4 groups in patients with SAPH receiving multiple different treatment regimens[23]. The current study demonstrates an even more dramatic survival difference based on the presence of fibrotic lung disease in patients treated with epoprostenol at a single center. The pathophysiology of SAPH is complex and further studies are needed to explore the mechanism by which fibrotic lung disease increases mortality in SAPH.

Despite classification as Group 5 PH, it is clear that some patients with SAPH exhibit similar hemodynamic profiles as patients with Group 1 PH (IPAH) and respond to PH-specific therapy in a similar manner. In fact, the existent literature does suggest that PH-specific therapy can improve SAPH in some patients. For example, in a study of 13 subjects with severe SAPH treated with either systemic epoprostenol or treprostinil, the 9 subjects who survived one year exhibited hemodynamic and functional improvements similar to those observed in this study as well as in our previous report[16, 17]. The effect of oral PH-specific medications has also been studied in SAPH, but has yielded mixed results[12, 24, 25]. In the largest study, bosentan was effective in treating patients with SAPH[21]. However, the PH in patients in studies of oral therapy was significantly less severe than in the patients in the current study. Thus, prostanoids may be preferable in the treatment of severe SAPH.

The current study compared survival between SAPH and IPAH and found it to be similar. In previous studies, SAPH survival has been reported at 50-59% at 5 years[7, 16, 26]. Indirect comparison of IPAH and SAPH suggests that 5 year survival is somewhat similar[27, 28]. Observations by us and others might suggest that there exists a sub-group of SAPH patients, more likely nonfibrotic patients, who respond better to prostanoid therapy. However, Bonham et al described a similar cohort demonstrating significant early mortality in a cohort with 77% of patients

having Scadding stage 4 disease; yet, not surprisingly, those patients who survived to long-term evaluation demonstrated significant improvements in hemodynamics[17].

This study has several limitations: 1) a relatively small sample size; 2) the retrospective nature; and 3) potential bias in the choice of patients treated with epopprostenol. However, the study does demonstrate long-term efficacy of epoprostenol therapy in patients with severe SAPH. Although patients with sarcoidosis may be a heterogeneous group in regard to the pathophysiologic mechanisms of PAH, all SAPH patients in this cohort were responsive to epoprostenol therapy, demonstrating significant improvement in hemodynamics and functional class. Surprisingly, in this cohort, patients with SAPH treated with epoprostenol had similar survival as a hemodynamically-matched IPAH cohort treated at the same center. Subgroup analysis identified Scadding stages 1-3 classification as having significantly improved survival over Scadding stage 4 and IPAH. These data suggest that epoprostenol is an effective vasodilator in patients with SAPH, should be considered in patients with severe SAPH, and identifies a SAPH subgroup which may uniquely benefit from prostanoid therapy. As such, further study is warranted in patients with SAPH to define those populations that are likely to be responsive to vasodilator therapy.

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The effect of the walk-bike on quality of life and exercise capacity in patients with idiopathic pulmonary fibrosis: a feasibility study

Monique Wapenaar[1], Elisabeth Bendstrup[2], Maria Molina-Molina[3], Maarten K.N. Stessel[4], Jasmina Huremovic[4], Eric W. Bakker[5], Isabella Kardys[6], Joachim G.J.V. Aerts[1], Marlies S. Wijsenbeek[1]

[1] Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands; [2] Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus; [3] ILD Unit, Hospital de Bellvitge-IDIBELL, University of Barcelona, Spain; [4] Department of Respiratory Diseases, Aalborg University Hospital, Aalborg, Denmark; [5] Division Clinical Methods and Public Health, Academic Medical Center, University of Amsterdam, the Netherlands; [6] Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands

Abstract. Idiopathic pulmonary fibrosis (IPF) is characterized by progressive loss of pulmonary function and exercise capacity, leading to loss of quality of life and often social isolation. A new walking aid, the walk-bike, showed an improvement in exercise performance in COPD patients. Aims of this pilot study were to evaluate feasibility of a homebased walk-bike intervention study in IPF patients and to explore the effect of the walk-bike on quality of life (QoL) and exercise capacity. Twenty-three patients with IPF were included in a randomized multicenter crossover study with 8 weeks of standard care and 8 weeks of walk-bike use at home. Ten patients completed both study phases. Study barriers included reluctance to participate and external factors (e.g. weather and road conditions) that hampered adherence. Patients' satisfaction and experience with the walk-bike varied greatly. After training with the walk-bike, health-related QoL (St. George's Respiratory and King's Brief Interstitial Lung Disease questionnaires) demonstrated a tendency towards improvement, exercise capacity did not. A clinically important difference was found between 6-minute walk test with the walk-bike and the standard test; median (range) respectively 602 m (358-684) and 486 m (382-510). Conclusions: Due to practical barriers a larger study with the walk-bike in patients with IPF seems not feasible. Individual patients may benefit from the use of a walk-bike as it improved action radius and showed a tendency towards improvement in QoL. No effect on exercise capacity was observed. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 192-202)*

Key words: Idiopathic Pulmonary Fibrosis, Home-based training, Quality of Life, Exercise training, Exercise capacity

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive and life-threatening disease of unknown cause (1). Symptoms such as dyspnea, cough and fatigue lead to a reduction of daily physical activities, exercise tolerance, muscle strength and quality of life (QOL). Problems reported by IPF patients are social isolation, increased level of dependency and immobility (1-5).

Pharmacologic treatment options are limited (5). There are two drugs that reduce pulmonary function decline in patients with IPF, however their effect on QoL is not convincingly established (6-8). In a selected, limited group of patients with IPF, lung transplantation can be an option. Non-pharmaco-

Received: 12 May 2020
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Correspondence: M. Wapenaar,
Department of Respiratory Medicine, Erasmus University Medical Center, Box 2040, 3000 CA Rotterdam, The Netherlands
E-mail: m.wapenaar@erasmusmc.nl

logic treatments that could improve QoL are increasingly investigated (4, 9-11). Pulmonary rehabilitation (PR) programs are recommended by expert opinion for the majority of IPF patients to improve QoL and exercise tolerance (1, 5, 12). Cochrane reviews on physical training in patients with different interstitial lung diseases (ILD), including IPF, indicate PR has a beneficial effect on QoL and functional exercise capacity in IPF patients (3, 13, 14). Another problem is that the long-term effects of PR are debated (15-20). Furthermore, PR programs are offered in outpatient clinics and specialized rehabilitation centers with a duration of usually 6 -12 weeks (14). Due to the limited life expectancy of IPF patients and practical problems with decreased mobility and transport, patients are often hesitant to participate in these external programs. Therefore, in recent years home-based (supervised) training has become increasingly investigated (20-22). An earlier study has demonstrated that a new-walking aid, the walk-bike , improved exercise performance in Chronic Obstructive Pulmonary Disease (COPD) patients due to the more efficient way of moving without excessive metabolic demand (23). To assess whether a study using this new method for homebased training is feasible and of benefit for IPF patients, we designed a crossover pilot study. We hypothesized that use of this walk-bike in daily life extends the range and everyday mobility of IPF patients, thereby decreasing the level of dependency and social isolation and improving QoL. If daily activities of IPF patients increase, exercise capacity might improve too. The objectives of this pilot study were (1) to evaluate the feasibility of a home-based walk-bike intervention study in IPF patients, and (2) to explore the effect of the walk-bike on QoL and exercise capacity.

Methods

Subjects

Patients were eligible to participate in this study if they were diagnosed with IPF according to the international guidelines criteria (1), had a diffusing capacity of the lung for carbon monoxide (TLCO) ≥ 25% predicted, a Forced Vital Capacity (FVC) ≥ 50% predicted, a 6-minute walk distance (6MWD) ≥ 150 meters and were clinically stable without a decline in TLCO and FVC of 10% or more in the past six months.

Exclusion criteria were participation in an official rehabilitation program 4 months preceding enrolment, musculoskeletal disorders, severe cardiac diseases (an ejection fraction < 30%, daily angina, or otherwise specified by treating cardiologist), unable to understand informed consent or other conditions that could hamper the use of a walk-bike. Patients were recruited at the outpatient clinics of three respiratory medicine departments in the Netherlands, Denmark and Spain (NTR5334, www.trialregister.nl). The study was approved by ethic committees of all participating sites and all patients gave written informed consent to participate (MEC-2014-047, Erasmus University Medical Center).

Study design

This prospective multicenter pilot study followed a 2-period crossover design with an intervention period and a control period of each 8 weeks. The intervention was a home-based training program using a walk-bike in daily life during 8 weeks, with the aim of a minimum of 1 hour per day. Patients were asked to record the time of real use of the walk-bike in a diary. At baseline, instructions and training were given. During the control period patients received standard treatment only. The walk-bike is an ambulation aid, a form of a bicycle but without pedals (Figure 1). By sitting on the seat the load on the muscles of ambulation is reduced which results in a lower cost of transport (oxygen uptake in mL/min per meter distance) (23).

Study procedure

Prior to randomization clinical stability was assessed by the physician. Pulmonary function and exercise performance were tested by spirometry, TLCO and 6MWT. Patients were randomly allocated to start with the intervention- or control period by an independent research nurse not involved in the study and using sealed nontransparent envelopes. Block randomization was used to ensure that the numbers of participants assigned to each group were equally distributed during the different seasons. After 8 weeks of intervention- or control period, patients were asked to cross over. Outcome variables were

Fig. 1. Walk-bike

measured at baseline, after 9 weeks and at the end of the study at 18 weeks. Pulmonary function tests including FVC and TLCO were done as part of the routine medical follow up of treatment.

Feasibility outcomes

Outcomes of feasibility comprised the number of patients assessed for eligibility, the proportion of patients that were randomized, the number of patients that finished both periods of the cross-over study and adherence with the intervention (1 hour use of the walk-bike per day). Throughout the study, comments and suggestions for improvement from patients and the medical team were collected to explore potential barriers of this study for future research. After the study, patients were asked about their experience and satisfaction with the use of the walk-bike. Feasibility outcomes of all patients that signed informed consent were used.

Patient-reported outcomes

The primary outcome was change in total score in health-related QoL measured with the St. George's Respiratory Questionnaire (SGRQ) after 8 weeks of standard of care and after 8 weeks of walk-bike use at home. Although designed for patients with obstructive disease, the SGRQ has been found to be a valid measure of health-related QoL in patients with restrictive disease including IPF (24, 25). A change of 7 points in SGRQ total score (0-100) is known to be the minimal clinically important difference (MID) for IPF patients (26). Secondary outcome was change in total score of the disease-specific King's Brief Interstitial Lung disease health status questionnaire (K-BILD) (27). The MID range in ILD for the total score is 6-10 units (28).

Other secondary outcomes are change in SGRQ and K-BILD domain scores, and in scores measured with the General Anxiety Disorder Screener (GAD-7) (29).

Exercise capacity

Additional secondary outcomes were change in functional exercise capacity, determined by the 6MWT (30) after 8 weeks of standard of care or 8 weeks of walk-bike use at home, and change in the number of steps per day as a proxy for daily physical activities, measured with a pedometer (Yamax Digi-walker SW-200)(31). To compare exercise performance with or without the walk-bike, patients were asked to perform an additional 6MWT using the walk-bike, after the regular 6MWT. This was done at the visit after the intervention period (in week 9 or week 18 depending on allocation). The assessor that measured the regular 6MWT at 9 and 18 weeks was blinded for the allocation and patients were instructed not to inform the care provider. Patients were asked to wear the pedometer for a week at baseline, at the crossover moment and after the study.

Pulmonary function tests

PFT's were performed according to ATS/ERS 2005 criteria(32, 33). FVC and TLCO were recorded and expressed as percentage of the predicted value (%pred).

Analysis

Due to the explorative nature of this pilot study, no sample size calculations were done and results are given in a descriptive way. As it concerns a small group of patients, results are described without statistical analysis.

Results

Feasibility outcomes

One hundred and twenty five outpatients with IPF were assessed for eligibility for the study, 23 (18%) were interested in participating, signed informed consent, and were randomized. Twelve patients were allocated to start in the intervention group and 11 patients to the control group. Sixteen patients finished the first phase of 8 weeks of the study and after crossover, 10 patients also completed the second phase. Two patients who started in the intervention group did not crossover because they wanted to continue using the walk-bike. Other reasons for not completing the full protocol are shown in Figure 2**.**

Ten of the 14 patients that completed the walk-bike period, recorded the actual use of the walk-bike in a diary; the median (min-max) use of the walk-bike was 5.3 (2.0- 6.9) days a week and 43.9 (11.3-60.6) minutes per actual usage day. An overview of potential barriers and solutions as reported by patients and medical staff during this study is provided in Table 1.

Patient satisfaction and experience with the walk-bike are shown in Table 2. Comments differed from very satisfied with continuation of using the walk-bike after the study, to not satisfied because using the walk-bike was too heavy or because of feelings of embarrassment.

One patient reported two fall-incidents due to wet and slippery roads, without any physical complaints, and decided to stop with the study.

Explorative outcomes

Baseline characteristics (Table 3) demonstrate

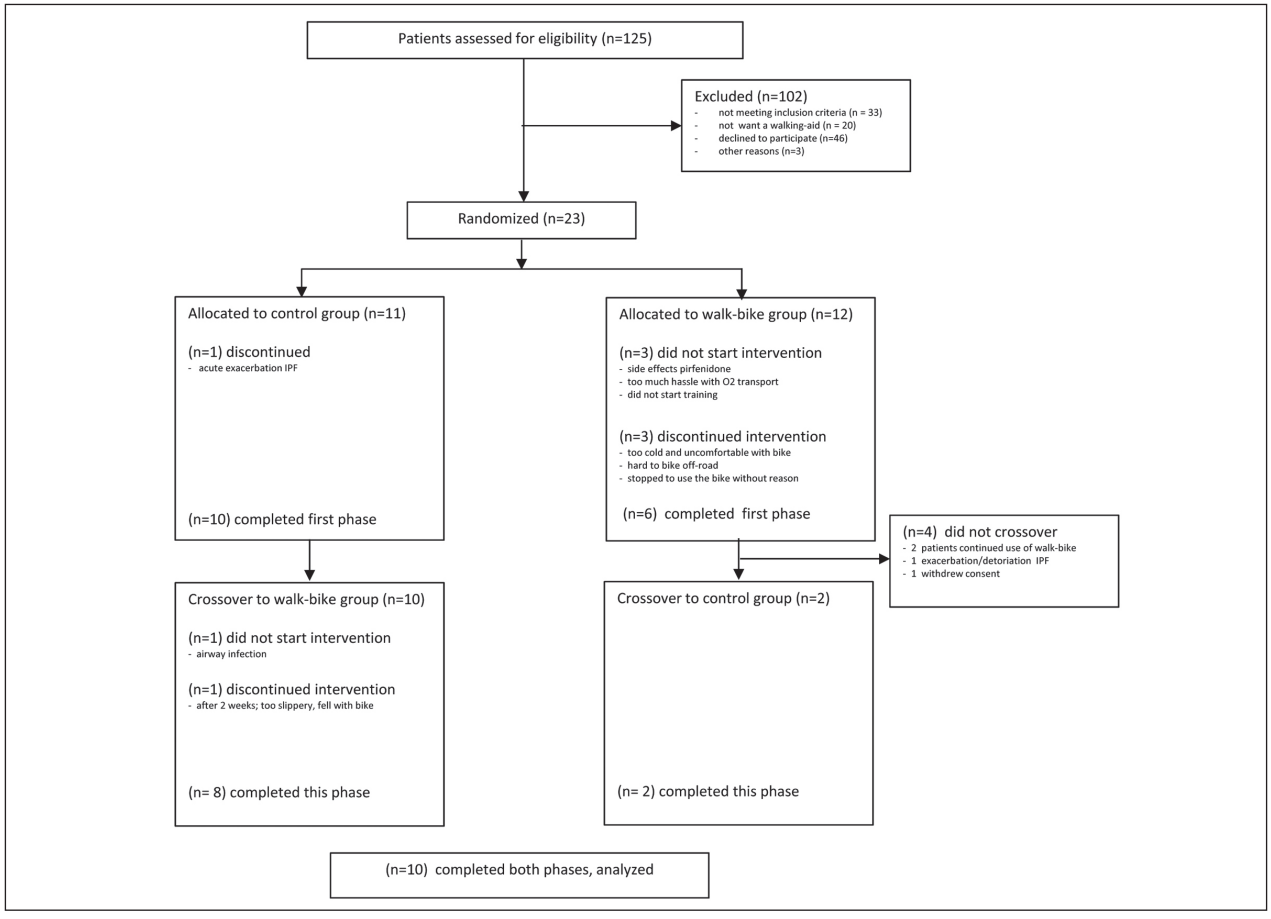

Fig. 2. Study flow chart of patients screened and enrolled

Table 1. Overview of detected potential barriers for homebased use of the walk-bike for research as detected by patients and the medical team

Potential barriers	Findings in this study	Possible solutions
Weather conditions	Patients frequently recorded not using the bike due to rain, storm, snow, slipperiness, heat and humidity.	Additionally offering a homebased indoor trainings program
Transport of oxygen device (a small bottle of oxygen can be attached with Velcro to the rear of the frame below the saddle).	One patient stopped 1 week after the start because he experienced attaching the oxygen to the bike was too much hassle. Another patient solved her problem with transportation of the oxygen bottle by transporting a smaller oxygen device in a back pack.	Ask the vendor to add a larger basket at the rear of the bike to facilitate oxygen transport or providing the option of a back pack.
Hills and unpaved roads	A patient recorded that even a minor hill makes using the walk-bike heavier than regular walking. Another patient mentioned the walk bike is most useful when the road is smooth or goes downhill and uphill, it is useful as a support object, like a walker. Another patient living in the countryside stopped using the bike because it was too heavy to use on unpaved roads.	The walk-bike seems more fit for paved roads and flat countries. The option of electrical support to switch on would be an option to overcome hills.
Compliance/motivation	Some patients were very compliant and recorded they used the bike every day for at least 60 minutes, others were hampered by external factors or symptoms and didn't use the bike for days.	Using accelerometers and new e-health technologies may help the medical team to detect barriers in use of the walk-bike at an earlier stage enabling them to contact and coach or support the patient in finding solutions.
Fear of stigmatization	Some patients didn't want to participate as they (or their spouse) where being afraid to be stigmatized for using an assistive device.	For some patients the potential benefit of the walk-bike will not outweigh the impact of making their disease visible by using an assistive device. Similar findings have been reported for ambulatory oxygen and careful discussion may help but in the end it is the patient who decides.
Saddle pain	Some patients were bothered by saddle pain or felt the saddle was uncomfortable	Provide silicone gel saddles
Limitations to use the walk bike in public places and public transport	None of the patients mentioned these problems	Patients were provided with a card that the walk-bike is an assistive device in case they would get questions.

that patients were predominantly male with a decreased FVC, TLCO, exercise tolerance and health-related QoL. The patients who dropped out during the study showed on average worse scores in diffusing capacity, exercise measures and health status. The results of the 10 patients that followed the complete protocol are given in Table 4 .

SGRQ- and K-BILD total score, as well as the domain scores, tended to improve after training with the bike (Figure 3), with the most striking improvement in SGRQ symptoms- and K-BILD chest scores.

No change after training was observed in the 6MWD, the anxiety score or perceived health status (Table 4).

A meaningful difference in distance covered was found between the 6MWT performed with the walk-bike and the unaided 6MWT with a median (min-max) 6MWD of 602 meters (358-684) vs. 486 meters (382-510); (Figure 4). The lowest oxygen saturation during the 6MWT with the walk-bike and unaided did not differ with a nadir SpO2 of 86% (80-91) vs. 87% (78-90).

During the study, the lung volume remained stable with a median (min-max) FVC at baseline of 69%pred (53-87) vs. 70%pred (57-86) in week 18.

Table 2. Comments on the walk-bike

Positive comments
Bike is really good for training; feel fit after 8 weeks of training
Although not comfortable with the bike because of shoulder pain, would like to continue using it
Able to walk further with less dyspnea
Enables me to leave the house and e.g. go to the bakery without being dependent of my spouse
Easier and nicer to walk
Able to walk further; it is more comfortable and gives possibility to rest
The walk bike has been a good means of contact with other people, it has the interest of news.
Negative comments
Too heavy in combination with oxygen; difficult to use with oxygen bottle
Difficult way of making steps
Able to walk further because of better stability but feel embarrassed when using walk bike
Uncomfortable with bike, roads are too slippery
For small hills walking with the help of the walk-bike is more difficult than without

Table 3. Baseline characteristics of the study patients

	Randomized (N=23)	**Completed study (N=10)**	**Drop outs (N=13)**
Male	18 (78%)	8 (80%)	10 (77%)
Age (years)	71 (54-88)	71 (60-88)	72 (54-88)
Pulmonary function			
FVC (%pred)	69 (48-97)	69 (53-87)	72 (48-97)
TLCO (%pred)	43 (26-67)*	51 (26-62)	40 (26-67)**
Exercise measures			
6MWD (m)	443 (278-593)*	481 (360-540)	433 (278-593)**
Nadir SpO2 (%)	87 (78-96)*	89 (81-95)	85 (78-96)**
Average steps/day	3521 (478-9869)†	4016 (707-9636)‖	3185 (478-9869)††
Health status scores			
SGRQ total [0-100]§§	50 (16-62)‡	44 (32-52)¶	55 (16-62)‡‡
K-BILD total [0-100]‖‖	63 (30-83)*	66 (56-78)	58 (30-83)**
Perceived health status [1-5]¶¶	3 (2-4)§	3 (3-4)	3 (2-3)‡‡
GAD-7 [0 –21]***	2 (0-11)*	2 (0-8)	5 (0-11)**

Data are presented as absolute number (%) or median (min-max). FVC: forced vital capacity (% predicted), TLCO: diffusing capacity of the lung for carbon monoxide (%predicted), 6MWD: distance walked in a 6-minute walk test (meters), SpO_2: oxygen saturation from pulse oximetry measured during 6MWT, SGRQ: St George's Respiratory Questionnaire, K-BILD: King's Brief quality of life questionnaire for Interstitial Lung Diseases, GAD-7: Generalized Anxiety Disorder 7-item scale. *: n=22, †: n=17, ‡: n=19, §: n=21, ‖: n=7, ¶: n=8, **: n=12, ††: n=10, ‡‡: n=11, §§: SGRQ lower scores indicate better health-related QoL, ‖‖: K-BILD lower scores indicate worse health-related QoL, ¶¶: Assessed with the SGRQ, ***: GAD-7 higher scores indicate more anxiety.

Table 4. Change in health status and exercise measures of patients that completed both phases (N=10)

	ΔControl period	ΔWalk-bike period
SGRQ *		
Total (n=8)	1.2 (-12.3 - 8.3)	-7.1 (-17.8 - 5.9)
Symptoms (n=9)	6.7 (-22.7 - 38.9)	-7.9 (-42.6 - 16.0)
Activity (n=9)	0.0 (-18.1 - 6.3)	-5.2 (-14.2 - 1)
Impact (n=8)	0.3 (-12.3 - 8.9)	-7.4 (-22.3 - 9.9)
K-BILD †		
Total (n=8)	1.8 (-14.7 - 15.3)	6.5 (-10.0 - 29.4)
Chest (n=8)	0.0 (-25.0 - 25.0)	12.5 (0.0 - 37.5)
Breathlessness & activity (n=9)	0.0 (-29.8 - 14.9)	0.0 (-21.8 - 46.8)
Psychological (n=8)	0.0 (-11.1 - 23.5)	6.2 (-16.1 - 18.5)
Other		
GAD-7 (n=9)	0 (-2 - 6)	0 (-2 - 0)
Perceived health status (n=9) ‡	0 (-2 - 0)	0 (-2 - 2)
Exercise measures		
6MWD (m) (n=7)	-4 (-25 - 28)	-3 (-34 - 23)
Nadir SpO2 (%) (n=7)	-1 (-3 - 6)	-3 (-7 - 2)
Average steps/day (n=6)	132 (-903 - 3056)	-461 (-4335 - 1063)

Data are presented as median (min-max) [n]; FVC: Forced vital capacity (%predicted), TLCO: transfer capacity of the lung for carbon monoxide (%predicted), 6MWD: distance walked during 6-minute walk test, SpO2: oxygen saturation from pulse oximetry, SGRQ: St George's Respiratory Questionnaire (MID for total score is 7 points) , K-BILD: King's Brief quality of life questionnaire for Interstitial Lung Diseases (MID range for total score is 6-10 points), GAD-7: Generalized Anxiety Disorder 7-item scale. *: A negative change in SGRQ score indicates an improvement in health-related QoL, †: A positive change in K-BILD score indicates an improvement in health-related QoL, ‡: Assessed with the SGRQ.

Gas exchange parameters showed a tendency toward decline with a TLCO at baseline of 50%pred (26-62) vs. 45%pred (25-59) in week 18.

We also analyzed the data including the four patients that did not cross over; no changes in results were found.

Discussion

In this crossover pilot study, we explored the feasibility of a home-based walk-bike intervention study in IPF patients, and evaluated its effects on QoL and exercise capacity.

The feasibility outcomes demonstrate that a home-based walk-bike intervention study in its current design is difficult to accomplish. Potential barriers for feasibility of the study include reluctance to participate in the study, but also external factors such as weather and road conditions that may hampered adherence to the protocol. Patients satisfaction with the bike greatly varied. Despite the moderate usage intensity of the walk-bike, we found a tendency towards improvement in QoL after the 8-week homebased training program with the walk-bike. Functional exercise capacity did not change. Mobility increased with an average of 116 meters in distance covered when using the walk-bike during the 6MWT, compared to an unaided regular 6MWT. Use of the walk-bike proved to be safe.

A larger future RCT to detect clear walk-bike training-effects on QoL and exercise capacity does

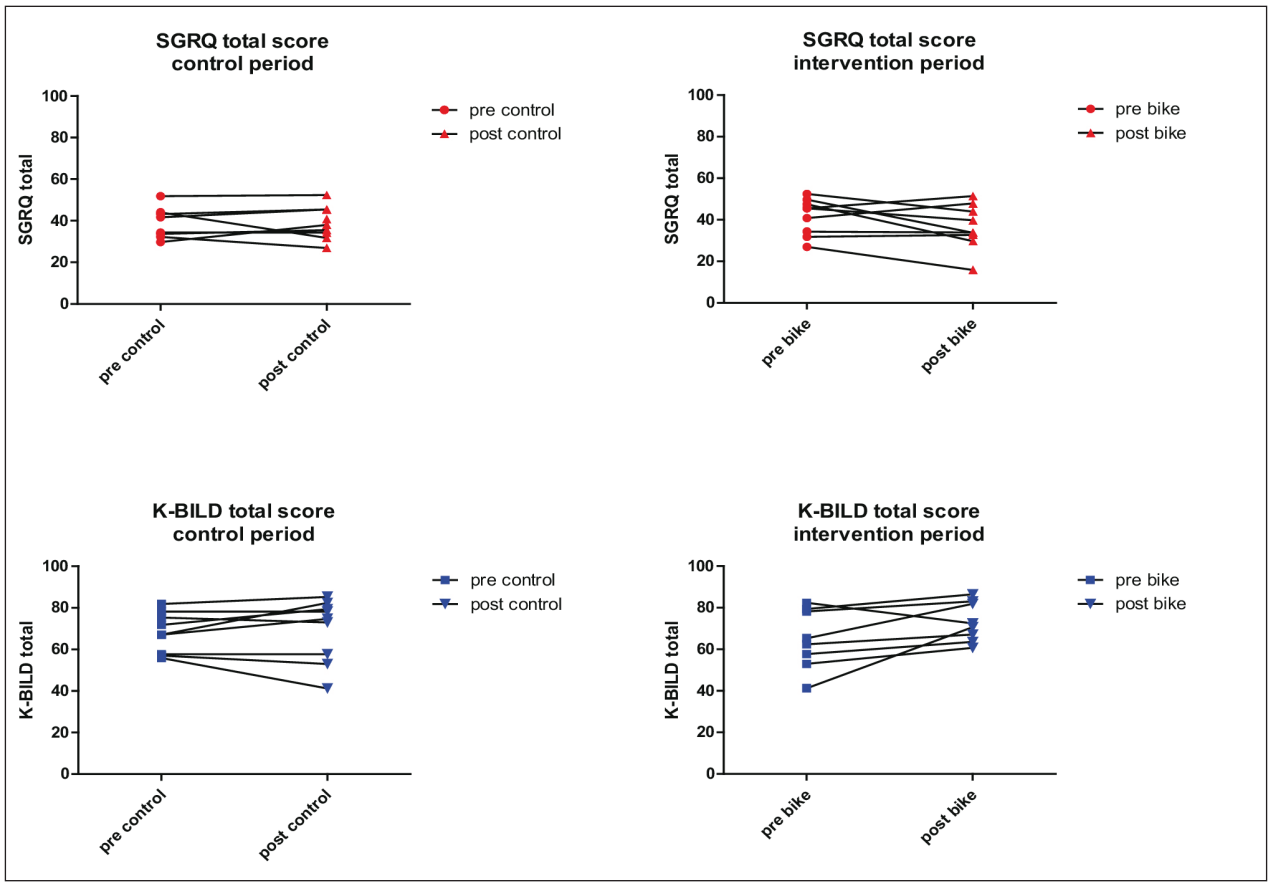

Fig. 3. Individual changes in SGRQ- and K-BILD total scores during control and intervention period. A negative change in SGRQ score indicates an improvement in health-related quality of life, a positive change in K-BILD score indicates an improvement in health-related quality of life

not seem feasible unless potential barriers detected in our study are being solved. We chose a crossover design as it holds the advantage over a parallel study that the patient is its own control, thereby reducing the influence of confounding variables. However, this crossover design warrants a longer duration of study for the individual patient (16-18 weeks). Despite the block randomization to account for seasonal changes, weather changes during the study period turned out to affect the use of the walk-bike. A study incorporating both walk-bike use as well as a home-based indoor training alternative, maybe a better design for a home-based training program. As table 1 shows, another potential barrier is the collection of correct information of the intensity of training. In our pilot study patients recorded the time of walk-bike use in a diary. However, this patient-recorded time may have included time spent waiting and resting on the bike without movement. Accelerometers are devices that if worn by the patient, can record intensity duration and frequency of activities and makes assessments of the potential effects of the walk-bike more accurate.

Patient satisfaction with the walk-bike varied greatly from positive to negative. Patients positively evaluated the walk-bike because it enabled them to walk further with less dyspnea, or made it possible to leave the house again. The feeling of an increased level of independence and social participation are both important aspects of IPF patients' QoL (9, 34).

Negative comments related to being afraid to be stigmatized when using the walk-bike. Swigris et al. investigated how IPF affects QoL from patients' perspective and noted many patients feel the need to try to hide the fact that they have a chronic illness when they are in public (34). This aspect, together with unfamiliarity with this new walking-aid, may also have

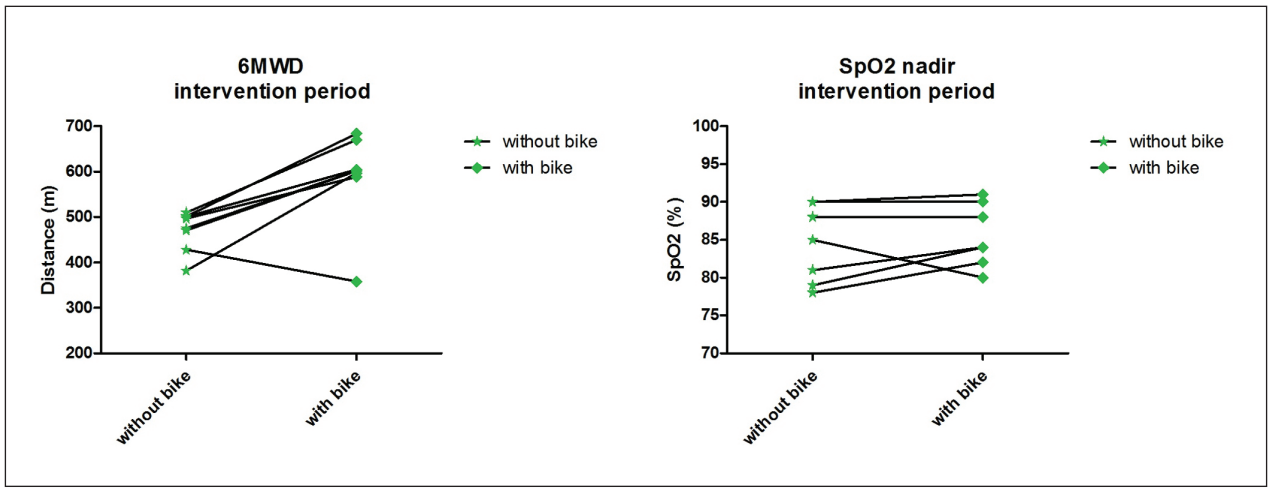

Fig. 4. Individual differences in 6MWD and lowest SpO2 during 6MWT with and without walk-bike

played a role in the difficult inclusion of patients in our study. Other patients noted that the walk-bike was too heavy when used outdoors e.g. on hilly roads. It might well be that when the road includes obstacles or hills, use of the walk-bike is more complicated, which was also observed in another study (35).

In this pilot study, the use of the walk-bike led to improvement of the SGRQ total equal to the minimal important difference (MID) of 7 points, with a median difference in change of 8.3 points between the intervention period and control period. This improvement in SGRQ scores is comparable with the effects reported in a recently published systematic review on PR in IPF.(36) Meta-analysis on the results of three studies demonstrated a weighted mean difference SGRQ total score of -8.34 (95% CI, -11.30 - -5.39; n = 82) between intervention -and control groups, favoring PR. In our study, we also assessed QoL with the ILD specific K-BILD questionnaire and found similar results in magnitude and direction of changes compared to the SGRQ. The K-BILD holds advantages for clinical use, being much shorter and disease specific.

We found no effect in exercise capacity (6MWD). In studies that assessed the effect of exercise training or PR programs in patients with IPF, 6MWD usually improved (14). The previous mentioned review of Gomes-Neto et al. (36) showed a weighted mean difference in 6MWD of 44 meters (95% CI, 5.3-82.8; n = 113) favoring PR. Most PR- or physical training programs contain supervised exercise protocols with a combination of endurance and resistance training (37). In our walk-bike intervention, the primary aim was to increase QoL. Participants were encouraged to use the walk-bike for at least one hour daily, and it was up to the discretion of the patients whether to use it continuously or in intervals. Practical factors such as weather conditions and day to day changes in wellbeing turned out to limit participants from using the walk-bike stringently and may have minimized the effect on exercise capacity. In patients with severe COPD it was shown that interval training at low burden could still have a positive effect on exercise capacity (38). We hypothesized that by increasing daily activities, patients would also exercise more at low burden which may eventually result in improving or maintaining exercise capacity and improving Qol.

The advantage of a home-based physical exercise program is increasingly recognized (14, 20). It remains to be evaluated if a more structured and supervised use of the walk-bike could play a role in such programs.

We found a meaningful improvement of 116 meters in distance covered during a 6MWT with use of the walk-bike, compared to an unaided test. This is in line with the improvement found by Vaes et al. who assessed the effects of the walk-bike on exercise performance in COPD patients (23). Improvement of mobility by using the walk-bike could potentially

lead to a higher level of independence and social participation. These factors may have been the main contributing factors to the tendency toward improvement in QoL in our study, even though exercise capacity did not improve.

One of the limitations of our study is the small sample size. We aimed to include 22 patients, enrolled 23 patients but after randomization, a part of the patients did not start or discontinued. Only 10 patients completed both phases which underlines the difficulties encountered when trying to set up an interventional study for such a vulnerable patient group. If patients still had a reasonably well-preserved exercise tolerance, they did not wish to use a walk-bike. On the other side, when patients were more impaired and wished to use the walk-bike, risk of dropout increased, leaving a small subgroup that potentially benefits from this intervention. A potential limitation of the study design could be a carry-over effect. However, we believe this can be neglected as 8 patients were allocated to the control period in the first phase and trained with the walk-bike in the second phase, only 2 patient participated in the reverse order. Moreover, with gas exchange parameters that tended to decline across the study, a potential order effect might have led to underestimation of the effect of the walk-bike. Furthermore, 2 patients that started with the walk-bike decided to continue with the walk-bike instead of crossing over to the control arm.

In conclusion, this pilot study showed that a larger RCT may not be feasible unless most of the potential barriers are being solved. Despite the small group studied we found that the use of a walk-bike led to a meaningful improvement in QoL for patients with IPF after an 8-weeks homebased training program. Use of the walk-bike also increased mobility for patients but did not result in an improvement in exercise capacity. Patient satisfaction varied greatly and the use of the walk-bike seems only beneficial for a small selected group of patients with IPF.

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Associations between interleukin 18 gene polymorphisms and susceptibility to vasculitis: A meta-analysis

Jae Hyun Jung[1,2], Han Saem Jeong[3], Sung Jae Choi[1,2], Gwan Gyu Song[1,4], Jong-Ho Kim[5], Tae Hyub Lee[6], Youngjin Han[7]

[1]Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul, 02841, Korea; [2]Division of Rheumatology, Department of Internal Medicine, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, 15355, Korea; [3]Heart Disease Research Institute, Dr. Jeong's Heart Clinic, 224 Baekje-daero, Wansan-gu, Jeonju-si, Jeollabuk-do, 54985, Korea; [4]Division of Rheumatology, Department of Internal Medicine, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul, 08308, Korea; [5]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, 73 Goryeodae-ro, Seongbuk-gu, Seoul, 02841, Korea; [6]College of Medicine, Chung-Ang University, 84 Heukseouk-ro, Donjak-gu, Seoul 06974, Korea; [7]Division of Vascular Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Korea

Abstract. Interleukin 18 (IL18), a pro-inflammatory cytokine, affects the development and progress of vasculitis. The production, expression, and function of this cytokine are affected by polymorphisms of promoter region of the *IL18* gene. In this study, a meta-analysis of the associations between several *IL18* polymorphisms and susceptibility to vasculitis was performed. Published literature from PubMed and Embase were retrieved. In total, nine studies comprising 1006 patients with vasculitis and 1499 controls combined, and the investigating the rs187238, rs194618, and rs360719 polymorphisms of the promoter region of the *IL18* gene, were included in the meta-analysis. Pooled odds ratios (OR) and 95% confidence intervals (CI) were estimated with fixed-effects model or random-effects model. The recessive model of the rs194618 polymorphism was found to be significantly associated with a high susceptibility to vasculitis (OR = 1.54, 95% CI = 1.02–2.33, $P = 0.04$), especially in the Mongoloid race, where the *A* allele of rs194618 was associated with a low risk of the disease (OR = 0.77, 95% CI = 0.62–0.95, $P = 0.01$). By contrast, the rs187238 and rs360719 polymorphisms were not associated with this inflammatory condition. This meta-analysis showed that some *IL18* polymorphisms are associated with susceptibility to vasculitis. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 203-211)*

Key words: Vasculitis, Interleukin 18, Polymorphism, Meta-analysis

Introduction

Vasculitis is a heterogeneous disease that causes inflammation of the blood vessel walls and damage to the skin and other organ systems. It is classified into large vessel (e.g., Takayasu's disease and giant cell arteritis), medium vessel (e.g., Kawasaki disease), and small vessel vasculitis type (e.g., antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune complex vasculitis) depending on the size of the blood vessels affected, with Behçet's disease and Cogan's syndrome being included among the various types (1). Several cytokines and chemokines play a major role in the development and progression of vasculitis, although there are differences depending on the type of blood vessel affected (2, 3). The gene

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Correspondence: Youngjin Han
Division of Vascular Surgery, Department of Surgery,
Asan Medical Center, University of Ulsan College of Medicine,
88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Korea
Tel. +82-2-3010-1312
E-mail: medjin00@gmail.com

polymorphisms of these cytokines, including interleukin (IL) 1, IL6, and IL10, are also associated with susceptibility to vasculitis (1, 4, 5).

IL18, a member of the IL1 superfamily, is biologically and structurally related to IL1β, mediates the T-helper 1 (Th1)-polarized immune response, and promotes inflammation by enhancing the production of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and granulocyte-monocyte colony-stimulating factor (6, 7). IL-18 is associated with various diseases, including infections, inflammations, autoimmune diseases, and cardiovascular diseases (8, 9). Previous studies have shown that vasculitis is also associated with IL18, where serum levels of this cytokine were elevated in Behçet's disease and ANCA-associated vasculitis, which was associated with kidney involvement (10, 11). Polymorphisms of the *IL18* gene have been shown to be associated with elevated IL18 levels (12). The *IL18* gene is located on chromosome 11q22.2-22.3, and various polymorphisms in the promoter resion of this gene are associated with autoimmune diseases (13). Among the polymorphisms of *IL18*, those at positions rs187238 (-137 G/C) and rs194618 (-607 C/A) have been studied the most (14-16). Nonetheless, there are some published studies on polymorphisms at other positions, such as rs549908 (+105 A/C), rs1946519 (-656 T/G), and rs360719 (-1297 T/C) (17-19).

Although published studies on the association between *IL18* polymorphisms and vasculitis are available, the types of vasculitis and promoter regions analyzed were different, and the results were different as well (6, 7, 20-27). In this present study, we performed a meta-analysis to investigate the associations between several polymorphisms of the *IL18* gene (rs187238, rs194618, and rs360719) and susceptibility to vasculitis.

Methods

Databases and literature sources

A literature search was performed for studies examining the association between *IL18* gene polymorphisms and vasculitis using the PubMed and Embase databases (up to January 2020). The following keywords and subject terms were used interleukin 18, IL18, polymorphism, variant, mutation, genotype, haplotype, vasculitis, arteritis, Takayasu, giant cell, Kawasaki, polyarteritis, polyangiitis, eosinophilic granulomatosis, purpura, Wegener, Churg-Strauss, Behcet, and ANCA. Additional studies not found in PubMed or Embase were manually obtained using citied references from included studies. No restrictions were placed on race, language, ethnicity, or geographical area.

Selection criteria and data extraction

The inclusion criteria for this meta-analysis were case-control studies that determined the distributions of the *IL18* gene polymorphisms and vasculitis, detailed data for both the case and control groups, and any other data from which the desired numbers could be calculated. Two or more studies of polymorphisms at the same position in the *IL18* promoter region were included. Studies were excluded on the basis of the following criteria: those that contained overlapping data; studies in which the number of null and wild genotypes or alleles could not be ascertained; and investigations that were review articles or contained only abstracts. We extracted the author, year of publication, country of the study subjects, number of cases and controls, Hardy–Weinberg equilibrium (HWE) *P* value, and the allele and genotype frequencies of the *IL18* polymorphism from each study. This meta-analysis was reported on according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines.

Statistical analysis

The allele counting method was used to determine the allele frequencies in the *IL18* promoter region. The meta-analysis was performed using Cochrane Collaboration RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The HWE *P*-value was estimated using Pearson's chi-squared test. The odds ratio (OR) and 95% confidence interval (CI) were used to determine whether there was evidence of an association between the respective *IL18* polymorphisms and susceptibility to vasculitis. The meta-analysis was also based on allele contrast and dominant, recessive, and homozygote models. The heterogeneity of the included studies was estimated

using Cochran's Q test and I^2 statistics. When the Q test was significant ($P < 0.05$) or $I^2 > 50\%$, the random-effects model was used; otherwise, the fixed effects model was used (28). Forest plots were drawn to visualize the overall effects. To overcome the heterogeneity observed in the meta-analysis, subgroup analysis by race and vasculitis type was performed. Funnel plots were generated and visually inspected for asymmetry to determine if there was any publication bias.

Results

Studies included in the meta-analysis

In total, nine studies (comprising 1006 patients with vasculitis and 1499 controls combined) were included in this meta-analysis. A flow chart detailing the inclusion and exclusion processes is shown in Figure 1. With regard to the promoter region of the *IL18* gene, there were nine studies on rs187238, eight studies on rs1946518, and three studies on rs360719. In terms of the races of the subjects studied, six studies were on Caucasians and three studies were on the Mongoloid race. With regard to the vasculitis type, there were six studies on Behçet's disease and one study each on giant cell arteritis, Kawasaki disease, and Henoch–Schönlein purpura. Additionally, a subgroup analysis was performed on Behçet's disease. Details of the *IL18* polymorphism studies are summarized in Table 1.

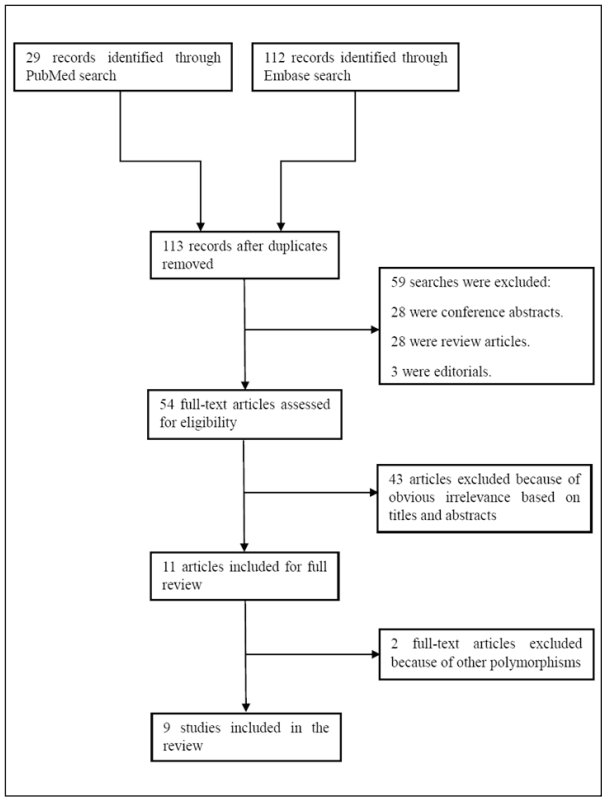

Fig. 1. Flow chart of the application of inclusion/exclusion criteria

Meta-analysis of associations between the IL18 polymorphisms and overall vasculitis

In the meta-analysis of associations between the rs187238 and rs360719 polymorphisms and vasculitis, both polymorphisms were found to be not significantly associated with the allele contrast and all genotypes. In the case of the rs194618 polymorphism, the recessive model was found to be significantly associated with susceptibility to overall vasculitis (OR = 1.54, 95% CI = 1.02–2.33, $P = 0.04$; Figure 2A), but not the allele contrast and other genotypes (Table 2).

In the subgroup analysis by race, both the rs187238 and rs194618 polymorphisms in Caucasians were not found to be significantly associated with susceptibility to vasculitis. In the Mongoloid race, rs187238 was also not significantly associated with susceptibility to vasculitis, whereas the *A* allele of rs194618 tended to be protective against the condition (OR = 0.77, 95% CI = 0.62–0.95, $P = 0.01$), with the recessive model showing a tendency to increase the susceptibility risk (OR = 1.99, 95% CI = 1.37–2.88, $P = 0.0003$; Table 3 and Figure 2B).

Meta-analysis of associations between the IL18 polymorphisms and Behçet's disease

A subgroup analysis of the associations of the rs187238 and rs194618 polymorphisms with Behçet's disease was performed (Table 4). There was no significant association found between susceptibility to Behçet's disease and the allele contrast and all genotype models of the rs187238 polymorphism. By contrast, for the rs194618 polymorphism, only the recessive model was found to be significantly associated with susceptibility to this disease (OR = 2.17, 95% CI = 1.54–3.06, $P = 0.04$; Figure 2C).

Table 1. Characteristics of the individual studies included in the meta-analysis

First author	Year	Country	Race	Disease	Promoter region	Number of cases	Number of controls	HWE *P*-value
Hazzaa	2014	Egypt	Caucasian	Behçet's disease	rs187238, rs1946518	80	80	0.590, 0.650
Vaccarino	2013	Italy	Caucasian	Behçet's disease	rs187238	32	128	0.560
Htoon	2011	Turkey	Caucasian	Behçet's disease	rs187238, rs1946518, rs360721	153	243	NA
Torres	2010	Spain	Caucasian	IgA vasculitis	rs187238, rs1946518, rs360722	62	200	0.101, 0.047, 0.344
Palomino-Morales	2010	Spain	Caucasian	Giant cell arteritis	rs187238, rs1946518, rs360723	212	403	0.221, 0.013, 0.346
Keskin	2009	Turkey	Caucasian	Behçet's disease	rs187238, rs1946518	123	101	0.001, 0.820
Hsueh	2008	Taiwan	Mongoloid	Kawasaki disease	rs187238, rs1946518	143	136	0.780, 0.267
Lee	2006	Korea	Mongoloid	Behçet's disease	rs187238, rs1946518	103	103	0.225, 0.934
Jang	2005	Korea	Mongoloid	Behçet's disease	rs187238, rs1946518	98	105	0.028, 0.000

HWE, Hardy–Weinberg equilibrium; NA, not applicable

Heterogeneity and publication bias

The genotypes of the control groups of two studies on the rs187238 polymorphism and of three studies on the rs194618 polymorphism were not in HWE. One study did not show HWE in all three promoter polymorphisms (Table 1). In the meta-analysis of the rs187238 polymorphism, the fixed-effects model was used because there was no significant heterogeneity found. By contrast, significant heterogeneity was found in the allele contrast and dominant model in the meta-analysis of the rs194618 polymorphism, and in the all genotype models in the analysis of the rs360719 polymorphism (Table 2).

Funnel plots were drawn for the meta-analyses of the rs187238 and 194618 polymorphisms to identify publication bias. The plots were generally symmetrical, with four on the left and five on the right in the plot for the rs187238 polymorphism, and five on the left and three on the right in the plot of the rs194618 polymorphisms (Figure 3).

Discussion

IL18 acts mainly as a pro-inflammatory cytokine, inducing IFN-γ. It stimulates Th1 cytokines, promotes the differentiation and immune response of Th1 cells, and up-regulates other cytokines such as TNF-α and IL1β (29). Being structurally similar to IL1, IL18 is related to this cytokine superfamily through their sharing of common signaling pathway. IL1 is also primarily a pro-inflammatory cytokine and is involved in the development of inflammation in various diseases. Single-nucleotide polymorphisms (SNPs), which are common in humans, are associated with the susceptibility and therapeutic responses to a variety of diseases (6). *IL1* polymorphisms have been found to be significantly associated with vasculitis, including Behçet's disease (4), and a previous meta-analysis showed that Behçet's disease was associated with *IL18* rs1946518 polymorphisms. Although vasculitis is a heterogeneous disease, polymorphisms of genes encoding inflammatory cytokines such as IL10, have been reported to be associated with overall vasculitis (5). Our present meta-analysis showed

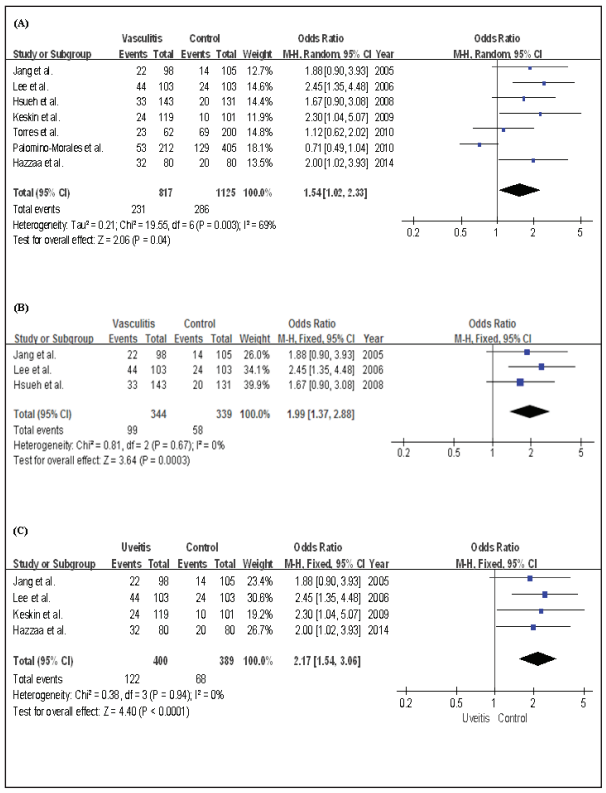

Fig. 2. Odd ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for determined of the association between the recessive model of the *IL18* rs194618 polymorphism and susceptibility to vasculitis. (A) Overall vasculitis. (B) Mongoloid race. (C) Behçet's disease. *IL18*, interleukin 18 gene.

a significant association between vasculitis and the *IL18* rs1946518 polymorphism, with the recessive model having a protective effect on the development of the disease, including Behçet's disease. However, the rs187238 and rs360719 polymorphisms were not associated with susceptibility to vasculitis. Although the *IL18* rs1946518 polymorphism is known to be associated with vascular diseases (e.g., coronary artery disease) and other diseases (e.g., cancer, asthma and tuberculosis), the relationships between the polymorphisms of the different promoter regions and each d,isease were different (17, 30-33). These results suggest that SNPs of the *IL18* gene affect the inflammatory process but act differently for each disease. Various factors, such as race and the environment, are related to SNPs.

Vasculitis chronically inflames the blood vessels through an autoimmune process, during which T-cell functional abnormalities occur (34). In particular, an imbalance between Th1 and Th2 cells occurs in vasculitis, and genetic variants of the Th1 and Th2 cytokines are closely related to the susceptibility to this inflammatory condition (21). The Th1 cytokine is representative of IL12 and IL18. SNPs of *IL18* are suggested to play a role in the development of vasculitis by affecting the imbalance between Th1 and Th2 cells. In addition to this Th cell imbalance,

Table 2. Meta-analysis of associations between the *IL18* polymorphisms and overall vasculitis

	Test of association			Test of heterogeneity		
	OR	**95% CI**	***P***	**Model**	***P***	***I²* (%)**
rs187238						
C vs. G	0.98	0.85–1.13	0.79	F	0.13	36
Dominant model	1.20	0.84–1.73	0.32	F	0.41	0
Recessive model	1.02	0.83–1.24	0.85	F	0.09	43
CC vs. GG	0.90	0.54–1.48	0.67	F	0.18	34
rs194618						
A vs. C	0.89	0.68–1.15	0.36	R	<0.0001	78
Dominant model	1.05	0.83–1.33	0.69	F	0.08	50
Recessive model	1.54	1.02–2.33	0.04	R	0.003	69
AA vs. CC	0.75	0.44–1.28	0.28	R	0.007	69
rs360719						
C vs. T	1.18	0.86–1.62	0.29	R	0.10	56
Dominant model	1.15	0.12–10.65	0.90	R	0.11	61
Recessive model	0.79	0.45–1.41	0.43	R	0.08	66
CC vs. TT	0.92	0.08–10.93	0.95	R	0.08	67

OR, Odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

Table 3. Meta-analysis of associations between the *IL18* rs194618 polymorphism and overall vasculitis according to race

	Test of association			Test of heterogeneity		
	OR	**95% CI**	***P***	**Model**	***P***	***I²* (%)**
Caucasian						
A vs. C	0.96	0.67–1.38	0.85	R	0.0002	82
Dominant model	1.12	0.64–1.95	0.70	R	0.03	67
Recessive model	1.30	0.73–2.30	0.37	R	0.010	74
AA vs. CC	0.74	0.31–1.78	0.51	R	0.002	80
Mongoloid						
A vs. C	0.77	0.62–0.95	0.01	F	0.34	9
Dominant model	1.10	0.74–1.64	0.63	F	0.39	0
Recessive model	1.99	1.37–2.88	0.0003	F	0.67	0
AA vs. CC	0.71	0.44–1.13	0.15	F	0.89	0

OR, Odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

Table 4. Meta-analysis of associations between the *IL18* polymorphisms and Behçet's disease

	Test of association			Test of heterogeneity		
	OR	**95% CI**	***P***	**Model**	***P***	***I²* (%)**
rs187238						
C vs. G	0.97	0.80–1.18	0.78	F	0.28	20
Dominant model	1.31	0.59–2.87	0.51	F	0.27	24
Recessive model	1.11	0.83–1.46	0.49	F	0.28	21
CC vs. GG	0.71	0.31–1.60	0.41	F	0.28	22
rs194618						
A vs. C	0.89	0.68–1.15	0.36	R	<0.0001	78
Dominant model	1.05	0.83–1.33	0.69	F	0.08	50
Recessive model	2.17	1.54–3.06	0.04	R	0.003	69
AA vs. CC	0.75	0.44–1.28	0.28	R	0.007	69

OR, Odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

distortions in the Th17 response and functional defects of regulatory T cells play roles in the pathogenesis of vasculitis, where cytokines such as IL4, IL17, IL10, and IL21 are involved in the immune response (34). In addition, our meta-analysis included mainly Behçet's disease, an inflammatory disorder that has been shown by a previous meta-analysis to be associated with *IL12B* polymorphisms aside from *IL18* polymorphisms. Because these various genes are involved in the susceptibility to vasculitis, gene–gene interactions should be considered. Environmental and genetic factors are also associated with susceptibility to vasculitis, with smoking, ultraviolet light and silica reportedly increasing the susceptibility risk

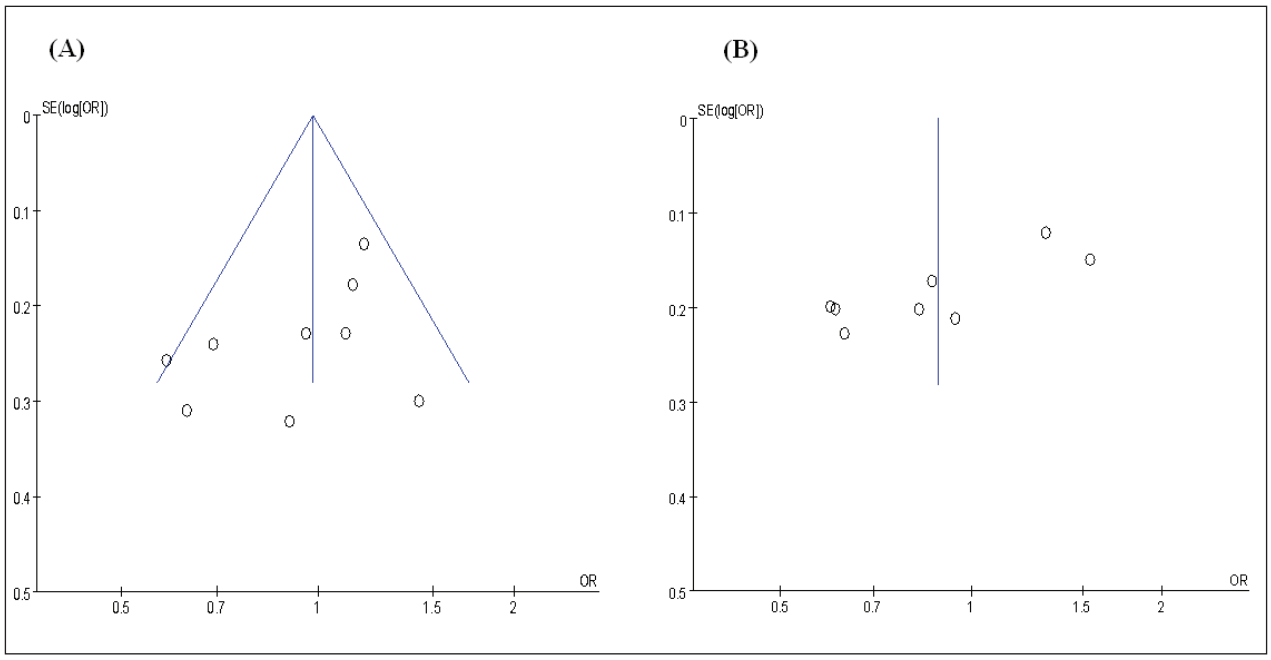

Fig. 3. Funnel plots for studies on *IL18* polymorphisms and susceptibility to vasculitis. (A) rs187238. (B) rs194618. *IL18*, interleukin 18 gene.

(35, 36); therefore, gene–environmental interactions should also be considered.

The effect of SNPs on diseases depends on the race of the patients. In this meta-analysis, *IL18* rs194618 polymorphisms were associated with the Mongoloid race, but not with Caucasians. The prevalence of each type of vasculitis was also different by geographical area, with that of giant cell arteritis being high in Scandinavians, that of Kawasaki disease being high in North-East Asians, that of IgA vasculitis being high in Britons and Spaniards, and that of Behçet's disease being high in Turks and Middle Eastern individuals (37). The difference in prevalence among different geographical areas can be influenced by both race and environmental factors, with Caucasians being distributed mainly throughout Europe, Northern Africa, and West Asia, whereas the Mongoloid race is distributed throughout East Asia and includes Native Americans. The differences between race-related SNPs and the susceptibility to diseases are important for identifying disease risk factors in each group and in planning health services.

This study is the first meta-analysis of the associations between vasculitis and *IL18* polymorphisms. However, the study had some limitations. First, vasculitis is a heterogeneous disease with multiple types being classified according to the size of the affected blood vessels. The clinical manifestations for each disease type and the therapeutic drug requirements are also different (38). Giant cell arteritis responds well to steroids and shows an effective response to tocilizumab; Kawasaki disease is mainly treated with aspirin and intravenous immunoglobulins; IgA vasculitis has no standard treatment; and Behçet's disease is treated with methotrexate or azathioprine, with TNF-α being used in special cases (38-40). However, vasculitis is commonly accompanied by skin lesions, and the damage and weakening of the blood vessel wall have a common effect in destroying the vessel functions (41, 42). In addition, subgroup analysis was performed on Behçet's disease, which belongs to various vessel vasculitis types. Second, there was heterogeneity in the studies included in the meta-analysis. Although most of the studies were consistent with HWE, some either did not display or were not consistent with HWE (Table 1). In addition, because some genotype models had heterogeneity, the random-effects model had to be used in

the meta-analysis (Tables 2, 3, and 4). However, we did conduct a subgroup analysis according to races for an analysis of heterogeneity, and confirmed differences between the Caucasian and the Mongoloid races in this regard. Third, aside from the disease susceptibility, these *IL18* polymorphisms may also be associated with the disease severity and treatment response; however, we did not perform a meta-analysis to determine this association. Finally, publication bias could not be completely excluded (Figure 3).

In conclusion, this meta-analysis showed that the *IL18* rs194618 polymorphism was significantly associated with susceptibility to vasculitis, especially Behçet's disease. According to race differences, this polymorphism was significantly associated with susceptibility to vasculitis in the Mongoloid race, but not in the Caucasians. However, owing to the small sample size and heterogeneity of the studies included in the meta-analysis, further studies are required.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2); 212-217 DOI: 10.36141/svdld.v37i2.9981

Role of alveolar collapse in idiopathic pleuroparenchymal fibroelastosis

Yoshiaki Kinoshita[1, 2], Hiroshi Ishii[3], Hisako Kushima[1], Masaki Fujita[1], Kazuki Nabeshima[2]; Kentaro Watanabe[4]

[1]Department of Respiratory Medicine; [2]Department of Pathology, Fukuoka University School of Medicine, Fukuoka, Japan; [3]Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, Fukuoka, Japan; [4]Department of Respiratory Medicine, Nishi Fukuoka Hospital, Fukuoka, Japan

Abstract. *Background:* Zonal aggregates of elastic fibres (zonal elastosis) and intraalveolar collagenosis with septal elastosis are histologic components of subpleural fibroelastosis of idiopathic pleuroparenchymal fibroelastosis (IPPFE). Zonal elastosis is considered to result from alveolar collapse, but this mechanism has not been fully justified. *Methods:* We immunohistochemically attempted to identify epithelial cells in zonal elastosis of 10 patients with IPPFE. The thickness of the zonal elastosis in relation to the total thickness of the fibroelastosis was examined to estimate the influence of zonal elastosis on the occurrence and development of IPPFE. *Results:* In 9 of the 10 patients, multi-cytokeratin-positive cells were found lining the inner surface of slit-like spaces embedded in the zonal elastosis. Zonal elastosis was predominant when fibroelastosis was < 1 mm thick but less predominant when it was ≥1 mm. *Conclusion:* The zonal elastosis was proven to result from alveolar collapse, which might be an initial lesion in IPPFE. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 212-217)*

Key words: zonal elastosis, intra-alveolar fibrosis, septal elastosis, two-layered pattern, elastic fibre

Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare subtype of idiopathic interstitial pneumonias predominantly located in the upper lobes, presenting with subpleural fibroelastosis with or without collagenous fibrosis of the visceral pleura (1-6). The most striking histology of PPFE is collagen-filled alveoli (intra-alveolar fibrosis) with septal elastosis (4). Furthermore, zonal or band-like dense aggregates of elastic fibres (zonal elastosis) in the subpleural areas are also key findings in PPFE (7-10). PPFE often shows a two-layered structure of fibroelastosis, with a subpleural layer of zonal elastosis and an inner layer of intra-alveolar fibrosis with septal elastosis (7-10).

Some investigators have speculated that zonal elastosis results from alveolar collapse (7-9). However, this speculation is not entirely convincing, as zonal elastosis usually consists of dense aggregates of elastic fibres without identifiable alveolar structures. Furthermore, the pathological process of fibroelastosis in PPFE remains unclear.

The present study therefore determined whether or not zonal elastosis is caused by alveolar collapse and speculated the role of zonal elastosis in the early stage of fibroelastosis in IPPFE.

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Correspondence: Kentaro Watanabe
Department of Respiratory Medicine, Nishi Fukuoka Hospital, 3-18-8 Ikinomatsubara, Nishi-ku, Fukuoka, 819-8555 Japan
Tel. +81 92 881 1331
E-mail: watanabe@fukuoka-u.ac.jp

Materials and Methods

Subjects

We retrospectively reviewed our clinical records between 1995 and 2017, and selected 18 patients with IPPFE who had been clinically diagnosed and pathologically confirmed according to the recently proposed criteria (8). We excluded six patients with non-PPFE fibrosis in the lower lobes based on radiologic (n=1), histologic (n=1), or radiologic and histologic assessment (n=4). We also excluded two patients in whom only one histologic specimen remained for the evaluation. Ultimately, 10 IPPFE patients without non-PPFE fibrosis in the lower lobes were eligible for the present study (pneumonectomy for lung transplantation, n = 2; surgical lung biopsy, n = 8).

Clinical and respiratory function data

Clinical data were collected from the patients' medical records. We evaluated the respiratory function parameters that had been measured less than one year before the histologic examinations, including the forced vital capacity (FVC), residual volume (RV), and RV/total lung capacity (TLC). The respiratory function data were expressed as absolute values (mL) and percentages of predicted values (% pred) (11).

Fibroelastosis pattern

Elastica van Gieson (EVG)-stained slides were scanned and converted to whole-slide images using NanoZoomer 2.0-RS (Hamamatsu Photonics, Hamamatsu, Japan). Each parameter was measured on the whole-slide images of all available specimens in each patient.

Zonal elastosis comprises a dense accumulation of elastic fibres without intervening collagen fibres (Fig. 1A). In lesions of intra-alveolar fibrosis with septal elastosis (IAFE), alveoli were filled with mature collagen (Fig. 1B and 1D).

We classified subpleural fibroelastosis into the following three patterns: (i) zonal elastosis not associated with IAFE; (ii) IAFE not associated with zonal elastosis; and (i+ii) a two-layered pattern comprising a subpleural layer of zonal elastosis and an inner layer of IAFE (Fig. 1C). The thickness of subpleural fibroelastosis was defined as the maximal distance from the outer elastic layer of the visceral pleura to the edge of the fibroelastosis, measured on a line running vertically from the pleura toward the inside (Fig. 1E). Using all specimens available, we measured the length of the pleura to which subpleural fibroelastosis (i, ii or i+ii) was attached to assess fibroelastosis quantitatively (Fig. 1C). The percentage of the total length of the pleura with each type of fibroelastosis to that with all types of fibroelastosis was calculated in each patient. After categorizing the pleura into two groups based on the thickness

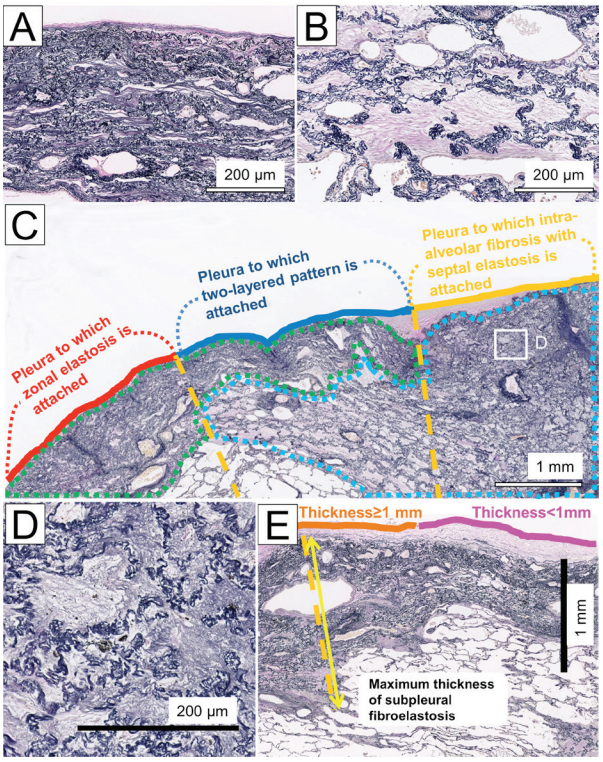

Fig. 1. Elastica van Gieson-stained sections in a patient with IPPFE. (A) Zonal elastosis. (B) Intra-alveolar fibrosis with septal elastosis (IAFE). Fibroelastosis in PPFE was segmented into zonal elastosis (green lesion) or IAFE (blue lesion) (C). We then determined the part of the pleura associated with zonal elastosis, IAFE, or a two-layered pattern involving zonal elastosis and IAFE. Each fibroelastosis pattern was decided on the orange-dotted vertical lines originating at the pleura and extending inward from the pleura. In this example, the percentages of the pleural length with zonal elastosis, a two-layered pattern, and IAFE were calculated to be 32.9%, 38.4%, and 28.8%, respectively. Fine elastic fibres are sometimes observed in old collagen-filled alveoli with septal elastosis (D, inset of C). (E) Maximal thickness of the subpleural fibroelastosis and pleura with subpleural fibroelastosis <1 mm or ≥1 mm thick

of subpleural fibroelastosis (pleura accompanied by fibroelastosis <1 mm or ≥1 mm thick), we compared the percentage of each type of fibroelastosis in each pleural group.

Immunohistochemistry

Immunostaining was performed on the specimens containing the zonal elastotic lesions using Multi-Cytokeratin (CK) AE1/AE3 (1:400 dilution; Leica Biosystems, Newcastle, UK) to identify cytokeratin-positive cells in the zonal elastotic lesions in each patient.

Statistical analyses

Continuous data are presented as medians and interquartile ranges in parentheses. Wilcoxon's signed-rank test was used to examine the difference in the percentage of fibroelastosis patterns. P<0.05 was considered to indicate statistical significance. All statistical analyses were conducted using the R software program (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Clinical characteristics of patients with IPPFE were as follows: 6 males and 4 females; mean age: 56.1 years old; range: 23-68 years old; body mass index: 16.3 (15.6-18.1) kg/m^2; Krebs von den Lungen-6: 374 (275-408) U/mL; FVC: 1980 (1350-2210) mL (65.5 [37.5-83.0]%); RV: 1690 (1028-1773) mL (94.3 [65.3-111]%) and RV/TLC: 0.41 (0.35-0.46) (118 [114-141]%).

Fibroelastosis pattern

A median of 5.2 specimens were available per patient for the histological examinations. The patterns of fibroelastosis in IPPFE patients are summarized in Table 1. The percentages of the length of the pleura with zonal elastosis, 2-layered pattern, and IAFE were 37.7% (33.0-46.6%), 40.4% (35.0-44.0%), and 19.1% (3.39-25.2%), respectively; the zonal elastosis and 2-layered patterns were more predominant than the IAFE pattern (p=0.01 and p=0.002, respectively).

The relationship between the thickness of fibroelastosis and the pattern of fibroelastosis

The average maximum thickness of subpleural fibroelastosis in each patient was 5.68 mm (range, 2.06-9.93).

In subpleural fibroelastosis <1 mm thick, the percentage of the length of the pleura with zonal elastosis (69.1% [54.7-87.9%]) was higher than that of the two-layered pattern (14.6% [1.88-23.2%]) (p=0.002) or IAFE (0% [0-18.4]) (p=0.004), whereas in subpleural fibroelastosis ≥1 mm thick, the percentage of the length of the pleura with zonal elastosis (33.0% [16.1-39.4%]) was lower than that pf the two-layered pattern (51.9% [44.4-59.9%]) (p=0.04) but higher than that of IAFE (14.0% [0-30.9%]) (p=0.002). Representative IPPFE cases are shown in Fig. 2.

Alveolar collapse in the zonal elastosis

Zonal elastosis was identified in 10 patients with IPPFE. Thickened elastic fibres ran parallel to the pleura in these lesions (Figs. 3A and 3B). The inner surfaces of the slit-like or small cystic spaces

Table 1. The patterns of fibroelastosis in IPPFE patients

Thickness of fibroelastosis \ Patterns of fibroelastosis	Zonal elastosis, %	Two-layered pattern, %	Intra-alveolar fibrosis with septal elastosis, %	P value†
Any thickness	37.7 (33.0-46.6)	40.4 (35.0-44.0)	19.1 (3.39-25.2)	1.00
<1 mm thick	69.1 (54.7-87.9)	14.6 (1.88-23.2)	0 (0-18.4)	0.002
≥1 mm thick	33.0 (16.1-39.4)	51.9 (44.4-59.9)	14.0 (0-30.9)	0.04

*The data are expressed as the group median (interquartile range).
†P-values were calculated for the comparison of the zonal elastosis and two-layered patterns.

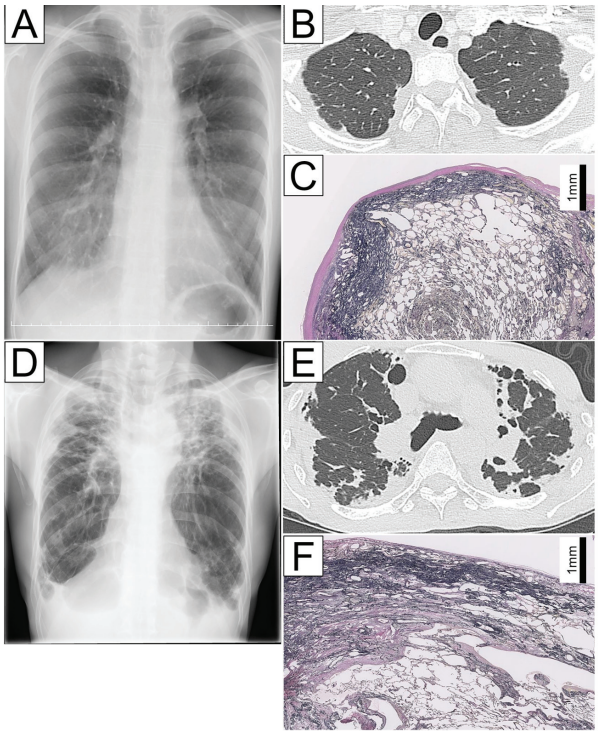

Fig. 2. Case 1 ***(A-C)***. Chest radiography and computed tomography findings for a 23-year-old female with IPPFE demonstrating modest wedge-shaped alveolar consolidation in the subpleural region of the upper lobes ***(A*** and ***B)***. An Elastica van Gieson-stained section of the upper lobe showing a zonal elastotic lesion ***(C)***. Case 2 ***(D-F)***. Chest radiography and computed tomography findings for a 64-year-old man with IPPFE demonstrating extensive wedge-shaped alveolar consolidation in the subpleural region of the upper lobes ***(D*** and ***E)***. An Elastica van Gieson-stained section of the upper lobe showing a two-layered fibroelastosis pattern ***(F)***.

positively reacted with CK AE1/AE3 in the zonal elastosis (Fig. 3C). Immunohistochemical positivity was identified in the zonal elastosis in 9 of the 10 patients with IPPFE.

Discussion

We found that CK AE1/AE3-positive cells lined the inner surface of the slit-like spaces embedded in the zonal elastosis in 9 of our 10 patients with IPPFE. Thus, the slit-like spaces were confirmed to be alveolar lumens that had been compressed or collapsed. The zonal elastosis in IPPFE was proven to result from alveolar collapse.

Disease progression of PPFE is characterised by increased thickness of subpleural fibroelastosis with a

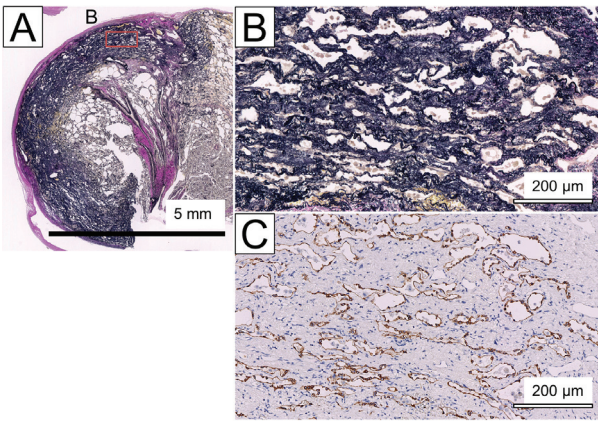

Fig. 3. An EVG-stained section (*A and B [inset of A]*) and a corresponding CK AE1/AE3-immunostained section *(C)*

volume loss of the upper lobes as well as caudal progression (5, 12). When the thickness of subpleural fibroelastosis was <1 mm, the percentage of the length of the pleura with zonal elastosis was much higher than that of the length of the pleura with the two-layered pattern. However, when the thickness of subpleural fibroelastosis was ≥1 mm, the percentage of the length of the pleura with a two-layered pattern was higher than that of the length of the pleura with zonal elastosis. Thus, fibroelastosis in patients with IPPFE may arise and progress in two stages (Fig. 4): the early stage, when the alveolar structure collapses and forms the zonal elastosis; and the advanced stage, when IAFE arises adjacent to the zonal elastosis, extending inward to form two-layered fibroelastosis.

Amitani et al.(3) recognized a flattened chest cage as a constitutional characteristic of patients with idiopathic pulmonary upper lobe fibrosis that is probably included in the broad concept of IPPFE nowadays, although it is not always constitutional but sometimes acquired and progressive in patients with idiopathic PPFE. Previously, we showed that the thoracic cage becomes flattened during the deteriorated course of PPFE (13). A narrowed thoracic space in PPFE could prevent lungs from fully expanding during inspiration, possibly resulting in the compression or collapse of subpleural alveoli, which may be functionally expressed by a marked decrease in FVC.

We previously reviewed four cases of PPFE in which surgical lung biopsies were performed twice at intervals (14). In two of these cases, the pathological

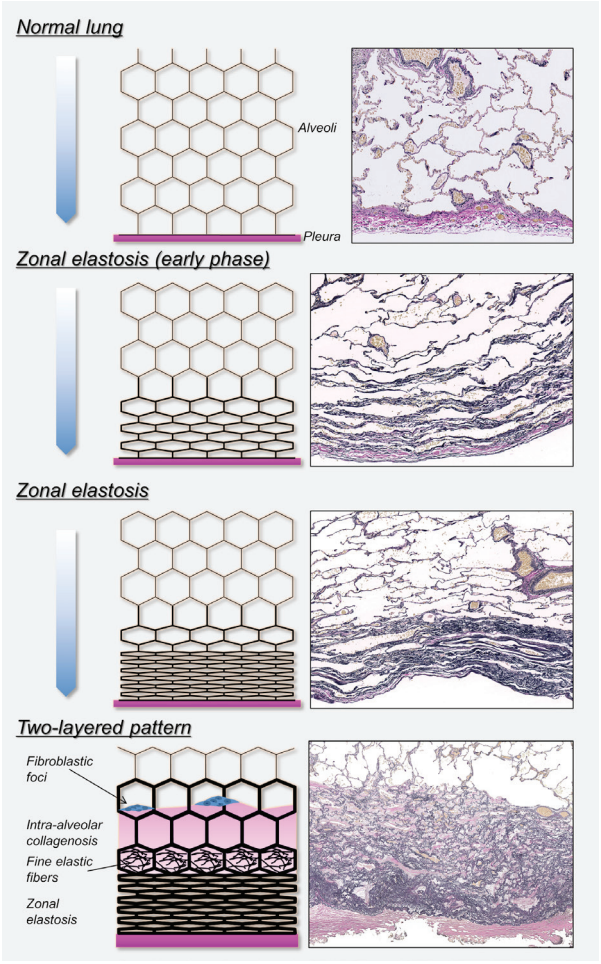

Fig. 4. A schematic overview of the disease progression hypothesis in IPPFE. The alveolar structure collapses, forming zonal elastotic lesions in the early phase of IPPFE. Consequently, intra-alveolar fibrosis with septal elastosis arises, progressing inward and forming a two-layered fibroelastosis pattern in IPPFE. Fine elastic fibres are sometimes observed in old collagen-filled alveoli with septal elastosis

diagnosis of the initial lung biopsy was cellular interstitial pneumonia with granuloma and cellular and fibrotic interstitial pneumonia, respectively. In both cases, the alveoli were not collapsed, but septal elastosis of the alveolar walls was already evident at the initial biopsy. However, the second biopsy showed subpleural zonal aggregates of elastic fibres, which suggested that alveoli with septal elastosis had been gradually compressed and shifted to subpleural areas, progressing to zonal aggregates of elastic fibres by the second lung biopsy. The histological changes in those two cases may support the present results, at least in part. Furthermore, in the present study, we proposed another possibility concerning the development of PPFE: lesions of intra-alveolar collagenous fibrosis with septal elastosis can arise adjacent to the pre-existing zonal elastosis.

The pathogenetic mechanism underlying intra-alveolar collagenosis in IPPFE is largely unknown. Jonigk et al. (15) presented an evolutionary model for the alveolar fibroelastosis pattern in stem cell transplantation-related PPFE: fibrin-rich exudates in the alveolar lumen lead to unsuccessful resolution by macrophages, resulting in fully remodelled alveolar fibroelastosis. The lymphatic vasculature plays a key role in tissue homeostasis of the lung (16). The excess protein-rich fluid that extravasates from the blood vessels returns to the blood circulation via the pleural or peri-bronchiolar lymphatics (17). We previously showed that the density and number of lymphatic vessels were significantly increased in the lesions of intra-alveolar collagenosis in PPFE, and lymphatic vessels were less frequently observed in the subpleural zonal elastotic lesions than in the lesions of intra-alveolar collagenosis (10). We speculate that the zonal collapse of the alveoli inhibits the innate lymphatic drainage of the lung via the pleural lymphatics. Increases in the density and number of lymphatic vessels in the lesions of intra-alveolar collagenosis may be compensatory mechanisms against decreased drainage via the pleural lymphatics.

Several limitations associated with the present study should be mentioned. First, this was a retrospective study conducted in a single centre, and the number of patients was small. Second, we investigated the histological fibroelastosis pattern in patients with IPPFE alone. The histological pattern in secondary PPFE may be different. Third, we proposed a potential mechanism underlying the development and progression of PPFE based on the histological findings of biopsied materials obtained from 10 patients with idiopathic PPFE, but we were unable to confirm the temporal changes in the histology of each patient. It will be necessary to establish animal models of PPFE to confirm this hypothesis.

In conclusion, zonal elastosis in IPPFE patients was shown to be associated with alveolar collapse. Early lesions of fibroelastosis in IPPFE might start with zonal elastosis.

Acknowledgement

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Compliance with Ethical Standards: The Fukuoka University Hospital Institutional Review Board approved the study protocol and waived the requirement for informed consent (approval number: 217M037).

Conflict of Interest: The authors declare no conflicts of interest in association with the present study.

Contributions: YK contributed to the design and concept of the study, data analysis, and writing of the manuscript. HI, HK, and MF contributed to the data analysis and final approval of the manuscript. KN contributed to the data analysis and gave advice on the design and concept of the study. KW contributed to the design and concept of the study, data analysis, and development of the manuscript.

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SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2); 218-224 DOI: 10.36141/svdld.v37i2.8587

Real world experience of response to pirfenidone in patients with idiopathic pulmonary fibrosis: a two centre retrospective study

James A. Eaden[1,2], Christopher M. Barber[2], Stephen A. Renshaw[1,2], Nazia Chaudhuri[3], Stephen M. Bianchi[2]

[1] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom; [2] Respiratory Medicine Department, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; [3] Interstitial Lung Disease Unit, University of Manchester NHS Foundation Trust, Manchester, United Kingdom

Abstract. *Introduction:* Pirfenidone has been shown to reduce the decline in forced vital capacity (FVC) compared to placebo in patients with idiopathic pulmonary fibrosis (IPF). Previous studies have suggested that patients with a more rapid decline in FVC during the period before starting pirfenidone experience the greatest benefit from treatment. The purpose of this retrospective observational study was to investigate the response to pirfenidone in IPF patients, comparing two groups stratified by the annual rate of decline in FVC % predicted prior to treatment. *Methods:* Using the rate of decline in FVC % predicted in the 12 months prior to pirfenidone, patients were stratified into slow (<5%) or rapid (≥5%) decliner groups. Comparisons in the lung function response to pirfenidone in these two groups were performed. *Results:* Pirfenidone resulted in no statistically significant reduction in the median annual rate of decline in FVC or FVC % predicted. In the rapid decliners, pirfenidone significantly reduced the median (IQR) annual rate of decline in FVC % predicted (-8.7 (-14.2 – -7.0) %/yr vs 2.0 (-7.1 – 6.0) %/yr; n=17; p<0.01). In the slow decliners, pirfenidone did not reduce the median (IQR) annual rate of decline in FVC % predicted (-1.3 (-3.2 – 1.3) %/yr vs -5.0 (-8.3 – -0.35) %/yr; n=17; p=0.028). *Conclusions:* We demonstrate the greater net effect of pirfenidone in IPF patients declining rapidly. We suggest that using an annual rate of decline in FVC of <5% and ≥5% may be useful in counselling patients with regard to pirfenidone treatment.*(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 218-224)*

Key words: idiopathic pulmonary fibrosis, pirfenidone, forced vital capacity, efficacy, treatment

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible interstitial lung disease (ILD) of unknown aetiology. Four large, multicentre randomised controlled trials (RCTs) have shown that pirfenidone is able to reduce the progression of IPF compared to placebo, as well as being safe and well tolerated (1-3). In 2013, the National Institute for Health and Care Excellence (NICE) in the United Kingdom approved the use of pirfenidone in IPF patients with a forced vital capacity (FVC) of 50-80% predicted (4). Nintedanib, a tyrosine kinase inhibitor, was approved by NICE for the treatment of IPF in 2016 (5).

Data from an interim analysis of a long-term, open-label extension study (RECAP) involving 603 patients who took part in the CAPACITY trials, showed that 69% of patients receiving pirfenidone were alive at week 228 (4.4 years) and that after five

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Correspondence: Dr James A. Eaden
Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom, S10 2JF

years, approximately half of the patients who were initially randomised to pirfenidone were still taking it (6). A pre-specified pooled analysis of 1,247 patients from the CAPACITY trials and the ASCEND study found that compared to placebo, pirfenidone reduced the risk of death at one year by 48% (7). It also demonstrated a consistent treatment effect across sub-populations, including those stratified by age and severity of disease.

RCTs of pirfenidone in IPF tend to poorly reflect patients treated in usual clinical practice. Study patients have less comorbidities, a specific severity of disease defined only by FVC and an age limit of less than 80 years of age. Open label studies and both prospective and retrospective reports of outcomes from usual clinical practice offer insights beyond those gleaned from RCTs.

A number of observational studies confirming the safety and efficacy of pirfenidone in patients with IPF in the real world have been published (8-21). Three of these have suggested that patients with a more rapid decline in FVC during the period before starting pirfenidone experience the greatest benefit from treatment determined by a significant improvement in FVC decline over a six month (10, 21) and a 12-month follow-up period (13).

In this retrospective observational study, we investigated the response to pirfenidone in patients with IPF, comparing two groups stratified by the annual rate of decline in FVC % predicted prior to treatment.

Methods

The article has been approved by Ethics Committee. We performed a retrospective observational study of IPF patients treated with pirfenidone in two tertiary referral centres for ILD in the North of England. The clinical records of 68 IPF patients commencing pirfenidone between June 2013 and March 2015 at the Northern General Hospital, Sheffield were reviewed. All patients fulfilled the NICE criteria of a FVC 50-80% predicted. The clinical records of 351 patients with IPF commencing pirfenidone between September 2011 and February 2016 at the Manchester University NHS Foundation Trust, Wythenshawe Hospital, Manchester were reviewed. These patients were either involved in the manufacturer-funded Named Patient Programme (NPP) for pirfenidone between September 2011 and April 2013 (n=48) or were treated after the approval of pirfenidone by NICE in April 2013 (n=303). Those patients involved in the NPP had a FVC of at least 50% predicted and/or diffusing capacity of the lungs for carbon monoxide (D_{LCO}) of at least 35% predicted. The patients who were treated following NICE approval had a FVC 50-80% predicted. All patients had a multidisciplinary team (MDT) diagnosis of probable or definite IPF as per the ATS/ERS consensus statement of 2011 (22).

Pirfenidone was prescribed as per manufacturer recommendations and was titrated to a dose of three 267mg capsules three times daily (total 2403mg/day), as tolerated. At each clinical review, details of any adverse event and the subsequent management strategy were documented. Dose modifications due to adverse events were implemented on an individual patient basis, according to the patient's response. Data regarding the number and type of adverse events were collected, including the number of patients who discontinued pirfenidone or had a change in treatment dose. Full blood count, urea and electrolytes and liver function tests were taken prior to commencing pirfenidone, and then monitored at each clinical review. Baseline demography collected included age, sex, body mass index (BMI), smoking status and comorbidities.

The annual rate of decline in FVC, FVC % predicted, D_{LCO} and D_{LCO} % predicted both pre- and post-pirfenidone was calculated using PFT data at 12 months pre-treatment, baseline and 12 months post-treatment. In those patients that did not have PFTs performed at 12 months pre- or post-treatment, using two or more PFT data sets (over a period greater than 12 months) a line of best fit was created using Microsoft Excel, which was then used to estimate the annual rate of decline in lung function. The absolute change in FVC% and D_{LCO} % predicted was used rather than relative change.

Patients were stratified into slow or rapid decliner groups according to the rate of decline in FVC % predicted in the 12 months prior to them receiving pirfenidone. Patients were defined as being slow decliners if they had a rate of decline in FVC % predicted of less than 5%. If the rate of decline in FVC % predicted was 5% or greater, they were designated as a rapid decliner. 5% was used as a cut off as a 2-6%

annual decline in FVC has been suggested as being clinically meaningful and noticeable by a patient in terms of symptom change (23). It also split the two groups into equal numbers of patients.

Wilcoxon signed rank or Mann-Whitney test was used to compare numerical variables that were not normally distributed and t-test was used to compare numerical variables that were normally distributed. Data were analysed in GraphPad Prism 7.0a. Parametric data are presented as mean ± standard deviation, unless otherwise stated. Non-parametric data are presented as median and interquartile range (IQR). P values <0.05 were considered to be statistically significant.

Results

Study population

In total, 419 IPF patients treated with pirfenidone were identified. However, only patients who had FVC data for at least 12 months prior to starting pirfenidone, at baseline (within one month pre/post treatment) and at least 12 months post-treatment initiation were included. As a result, 384 patients were excluded from the study as they did not have lung function data sufficient for a full evaluation. 309 patients (80.5%) were excluded due to the absence of PFT data at least 12 months pre-pirfenidone. This was due to these patients starting pirfenidone within 12 months from diagnosis. 53 patients (13.8%) were excluded due to the absence of PFT data at least 12 months post-pirfenidone. Reasons for the absence of this data include discontinuation of pirfenidone (n = 20) and death (n = 14). In 19 patients the PFT data was absent as the data was collected within 12 months of the patient commencing pirfenidone. 22 patients (5.7%) were excluded as PFT data was not available within one month pre/post treatment. One patient was excluded from the analysis as there was a 48% improvement in FVC over a 12-month pre-treatment period which is inconsistent with clinical behaviour and likely secondary to improved spirometry technique. Therefore, 34 patients were included in the study. Out of the 34 patients, 13 had the annual rate of decline in FVC% and D_{LCO} % predicted imputed from a line of best fit.

At the time of starting pirfenidone, the 34 patients had a mean age of 69 years (range 54-83). 71% were male. Mean BMI was 28.2 (range 18.7-36.7). 59% were ex or current smokers. Mean FVC was 2.6 ± 0.56L, mean FVC % predicted was 71.1 ± 7.2%, mean D_{LCO} was 3.7 +/- 1.1 mmol/min/kPa and mean D_{LCO} % predicted was 43.6 +/- 10.8% prior to pirfenidone therapy. Chronic obstructive pulmonary disease (COPD) was a documented comorbidity in 12% of patients prior to the diagnosis of IPF and therefore could represent combined pulmonary fibrosis and emphysema syndrome. Table 1 shows the baseline patient characteristics in our cohort compared to the CAPACITY (2) and ASCEND (3) studies.

Table 1. Baseline patient characteristics compared to CAPACITY and ASCEND studies

Patient characteristics	Total cohort (n=419)	Cohort analysed (n=34)	CAPACITY (n=432)	ASCEND (n=278)
Mean age - years	70.1	68.8	66.8	68.4
Male sex – no. (%)	338 (80.7)	24 (70.6)	306 (70.8)	222 (79.9)
Former / current smoker – no. (%)	278 (66.3)	20 (58.8)	399 (92.4)	184 (66.2)
Mean FVC % predicted	68.6	71.1	75.2	67.8
Mean D_{LCO} % predicted	40.3	43.6	47.1	43.7

Decline in PFTs

Pirfenidone treatment resulted in no statistically significant change in the median (IQR) annual rate of decline in FVC (-150 (-315 – -47.5) ml/yr vs -55 (-340 – 45) ml/yr; n=34; p=0.35), FVC % predicted (-4.5 (-9.3 – -1.3) %/yr vs -1.2 (-7.2 – 3.3) %/yr; n=34; p=0.16), D_{LCO} (-0.49 (-0.97 – 0.0075) units/yr vs -0.55 (-0.84 – -0.11) units/yr; n=24; p=0.89) or D_{LCO} % predicted (-6.6 (-10.8 – 2.6) %/yr vs -6.2 (-9.5 – -1.2) %/yr; n=24; p=0.96). Figure 1 shows the annual rate of decline in FVC % predicted pre- and post-pifenidone.

In the rapid decliners, defined as annual rate of decline in FVC ≥5%, pirfenidone significantly reduced the median (IQR) annual rate of decline in FVC (-310 (-480 – -220) ml/yr vs 20 (-285 – 140) ml/yr; n=17; p<0.01) and FVC % predicted (-8.7 (-14.2 – -7.0) %/yr vs 2.0 (-7.1 – 6.0) %/yr; n=17; p<0.01). There was no significant change in the median (IQR) annual rate of decline in D_{LCO} (-0.44 (-1.6 – 0.005) units/yr vs -0.81 (-0.86 – -0.15) units/yr; n=9; p=0.89) or D_{LCO} % predicted (-9.0 (-15.2 – 1.1) %/yr vs -8.1 (-10.6 – -1.0) %/yr; n=9; p>0.99). Figure 2 demonstrates the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the rapid decliners.

In the slow decliners, defined as annual rate of decline in FVC <5%, there was a statistically significant increase in the mean annual rate of decline in FVC (-70 (-115 – 20) ml/yr vs -180 (-350 – -25) ml/yr; n=17; p=0.005) and FVC % predicted post-pirfenidone (-1.3 (-3.2 – 1.3) %/yr vs -5.0 (-8.3 – -0.35) %/yr; n=17; p=0.028). There was no significant change in the median (IQR) annual rate of decline in D_{LCO} (-0.54 (-0.86 – 0.04) units/yr vs -0.46 (-0.71 – -0.05) units/yr; n=15; p=0.81) or D_{LCO} % predicted (-5.6 (-10.3 – 4.4) %/yr vs -4.9 (-8.0 – -0.5) %/yr; n=15; P>0.99). Figure 3 shows the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the slow decliners.

The baseline patient characteristics were similar between the rapid and slow decliner groups (table 2). Three patients in the rapid decliner group and four patients in the slow decliner group had either a dose reduction or a temporary discontinuation of pirfenidone due to side effects during the 12 months after commencing treatment.

Of the four patients with a documented comorbidity of COPD, two were rapid decliners and

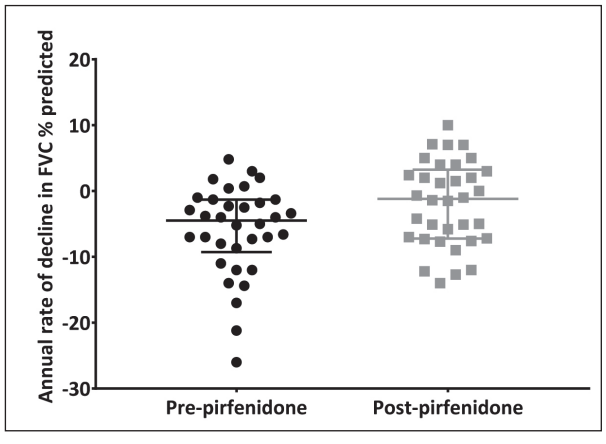

Fig. 1. Scatter plots (median and IQR) of the annual rate of decline in FVC % predicted pre and post pifenidone (p=0.16)

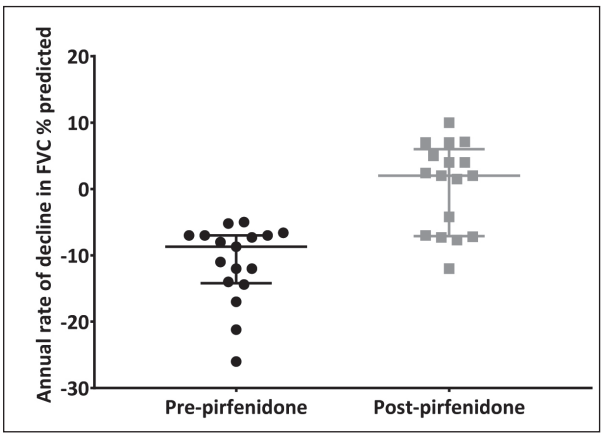

Fig. 2. Scatter plots (median and IQR) of the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the rapid decliners (p<0.01)

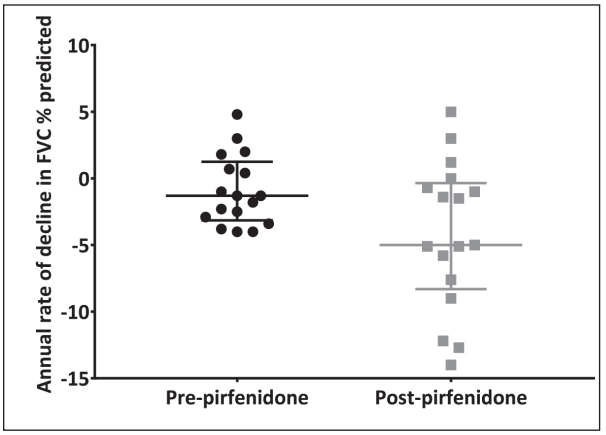

Fig. 3. Scatter plots (median and IQR) of the annual rate of decline in FVC % predicted pre- and post-pirfenidone in the slow decliners (p=0.028)

Table 2. Baseline patient characteristics of the rapid decliner and slow decliner groups (stratified using a pre-pirfenidone annual decline of FVC ≥5% versus <5%)

Patient characteristics	Rapid decliners	Slow decliners	p value
Mean age - years	68.9	66.9	0.45
Male sex – no. (%)	11 (64.7)	13 (76.5)	0.71
Former / current smoker – no. (%)	8 (47.1)	12 (70.6)	0.30
Mean FVC % predicted	70.4	71.7	0.62
Mean D_{LCO} % predicted	39.3	47.1	0.053

two were slow decliners. When these patients were removed from the above analysis there was no significant change to the results in terms of decline in FVC, FVC % predicted, D_{LCO} or D_{LCO} % predicted both overall and when stratified into slow or rapid decliner groups.

When the cohort of 34 patients were stratified into rapid and slow decliner groups using an annual rate of decline in FVC of ≥10% versus <10%, there was no statistically significant change in the median annual rate of decline in FVC or FVC % predicted pre- and post-pirfenidone in the slow decliners (n=26). However, in the rapid decliner group (annual rate of decline in FVC ≥10%) pirfenidone significantly reduced the median (IQR) annual rate of decline in FVC (-385 (-510 – -240) ml/yr vs 140 (50 – 280) ml/yr; n=8; p<0.01) and FVC % predicted (-14.2 (-20.2 – -12.0) %/yr vs 6.0 (2.1 – 7.1) %/yr; n=8; p<0.01). There was no statistically significant change in the median annual rate of decline in D_{LCO} or D_{LCO} % predicted pre- and post-pirfenidone in the slow decliners (n=20) or the rapid decliners (n=4).

Figure 4 is a linear regression XY graph of the annual rate of decline in FVC % predicted pre- and post-pirfenidone. The gradient of best fit is approximately -0.4 which means that for every 1% annual decline in FVC % predicted pre-treatment, there was a 0.4% greater response to pirfenidone. This is significantly non-zero with p=0.0084. Therefore, there is a significant negative correlation between the annual rate of decline in FVC % predicted pre- and post-pirfenidone.

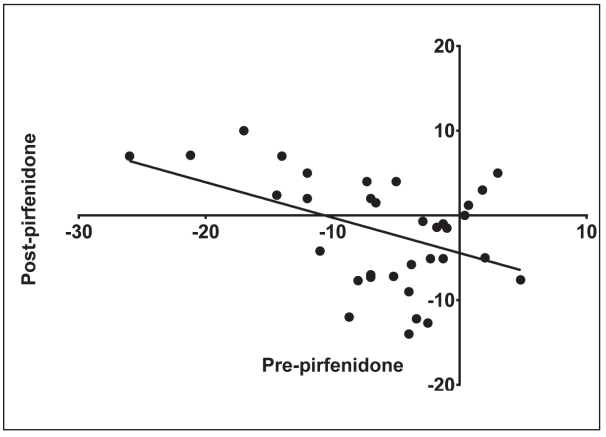

Fig. 4. Linear regression XY graph of the annual rate of decline in FVC % predicted pre- and post-pirfenidone (p=0.0084)

Discussion

This retrospective observational study from two tertiary referral centres for ILD in the North of England demonstrates the real world experience of pirfenidone treatment for a subset of patients with IPF in which lung function data was available at least 12 months pre- and post-treatment. IPF is generally a progressive disease with a variable clinical course which is often difficult to predict. Our data suggest that the rate of decline in FVC % predicted prior to starting pirfenidone can be used to stratify patients into slow (<5%/yr) and rapid decliners (≥5%/yr) and that the effect of pirfenidone is significantly different in these two groups. Our data demonstrate that pir-

fenidone significantly reduced the mean annual rate of decline in FVC % predicted and FVC in rapid decliners but not in slow decliners. In fact, there was a statistically significant increase in the mean annual rate of decline in FVC % predicted post-pirfenidone in the patients declining slowly. However, as demonstrated in figure 4, the FVC % predicted post-pirfenidone remained stable in the majority of the slow decliners. As pirfenidone treatment can be associated with a side effect profile it is important to attempt to identify those patients who will gain the best balance between benefit (in terms of reduced lung function decline) and potential harm (side effects). Therefore, we suggest that using a 5% annual rate of FVC decline cut off may be useful in making pirfenidone treatment decisions, especially in those patients where there are concerns regarding the benefit of treatment.

Nathan et al. have described, in post hoc analysis of the CAPACITY and ASCEND pooled data set, the inability of previous lung function to predict future lung function (24). This data analysis has been derived from static data points of FVC and FVC % predicted and has not considered rate of decline in FVC or FVC % predicted. However, our data analysis, although performed in much smaller numbers of patients, suggests that the rate of decline in lung function is an important consideration alongside static point measurement of FVC.

Three real life studies have shown similar results regarding the greater net effect of pirfenidone in IPF patients declining rapidly as compared with more slowly declining patients. A study by Okuda et al. demonstrated that patients who had the most severe decline in FVC (≥150 ml over a six-month period before starting pirfenidone) benefitted the most from treatment (10). Loeh et al. found that patients with an annual decline of FVC ≤10% prior to receiving pirfenidone remained stable with treatment, whereas those patients with an annual decline of >10% benefitted greatly from pirfenidone, with some patients experiencing an improvement in FVC (13). A similar outcome was demonstrated by Biondini et al. who also found that the beneficial effect from pirfenidone was greater in the patients with a pre-pirfenidone annual decline of FVC >10%, especially over the first six month treatment period (21). In addition to these studies, our results suggest that rapid decliners receive the most therapeutic benefit when the groups are stratified using a pre-pirfenidone annual decline of FVC ≥5% versus <5% as well as ≥10% versus <10%.

This study was retrospective and therefore limited mainly by our access to PFT data, both pre- and post-initiation of pirfenidone treatment, and the variation in testing and timing that often follows from usual clinical practice. Across the two centres, there were 419 IPF patients treated with pirfenidone over the study period. However, due to the lack of PFT data, 384 patients (92%) were excluded. This was mainly due to the absence of PFT data pre-pirfenidone, as many patients would have commenced treatment within 12 months of diagnosis. These patients that were excluded are more likely to have either rapidly progressive disease or a delayed diagnosis which is a potential source of bias. However, as illustrated in table 1, the lung function at the time of commencing pirfenidone was similar between the total cohort (n = 419) and the cohort with sufficient PFT data for analysis (n = 34). Another potential source of bias is the exclusion of patients that died or discontinued pirfenidone within 12 months of starting treatment.

Following initiation of pirfenidone, there was no statistically significant reduction in the median annual rate of decline in FVC or FVC% predicted in the total cohort. This may be due to the statistically significant increase in the median annual rate of decline in FVC and FVC% predicted post-pirfenidone observed in the slow decliner group. This has not been reported in previous studies of pirfenidone in IPF patients and is an interesting finding. However, this result is based on a small sample of a larger data set which is prone to bias and thus has a chance of being spurious. Therefore, it does not represent sufficient evidence for IPF patients with a slow rate of decline in FVC to be denied pirfenidone. The relatively small number of patients in our study necessitates caution when extending our findings to IPF patients in general and further prospective clinical studies, including larger numbers of patients are required before drawing any firm conclusions.

It could be argued that our data can be interpreted through reference to the statistical concept of 'regression to the mean'. This concept describes a bigger effect of a treatment in groups where high numbers of events are present e.g. the outcome of treatment of patients with high rate of decline in FVC will be greater than outcomes of treatment in patients with

slower FVC decline (less events). Although there is no specific statistical test that can confirm or refute this, the significant negative correlation between the annual rate of decline in FVC % predicted pre- and post-pirfenidone, demonstrated in figure 4 suggests that this is not the case.

In conclusion, we demonstrate a greater net effect of pirfenidone in patients declining rapidly as compared with more slowly declining patients. We suggest that using an incident rate of decline in FVC of <5% per year (slow decliners) and ≥5% per year (rapid decliners) may be useful in counselling patients with regard to treatment. However, we recognise the limitations of the study and suggest that larger studies are needed to confirm our findings before making significant changes to the routine management of IPF patients.

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Non-tuberculous, adenosine deaminase-positive lymphocytic pleural effusion: Consider immunoglobulin G4-related disease

Ori Wand[1,2,3], Benjamin D Fox2,[4], Osnat Shtraichman[1,2], Osnat Moreh-Rahav[2,5], Mordechai R Kramer[1,2]

[1] Pulmonary Institute, Rabin Medical Center, Beilinson Campus, Petach Tiqwa, Israel; [2] Sackler Faculty of Medicine, Tel Aviv University, Israel; [3] Pulmonary Division, Meir Medical Center, Kfar-Sava, Israel; [4] Pulmonary Institute, Assaf Harofeh Medical Center, Tzrifin, Israel; [5] Radiology Department, Edith Wolfson Medical Center, Holon, Israel.

Abstract. *Objective:* Immunoglobulin G4-related disease (IgG4-RD) is a recently described systemic disorder. Pleural effusion is considered an uncommon manifestation of the disease. We describe a case series of patients with IgG4-RD and clinically significant pleural effusions. *Methods:* A retrospective analysis of patients with histologically proven IgG4-RD treated for pleural effusion in our clinic. *Results:* We identified 4 male patients with pleural effusion caused by IgG4-RD. The effusions were lymphocytic exudates, with especially high protein concentrations. All patients had hyperglobulinemia, elevated serum immunoglobulin G (IgG) levels and elevated levels subclasses IgG1 and IgG4. In two patients, levels of adenosine deaminase (ADA) were measured in the effusion and were elevated (309 and 108 IU/L). Tuberculosis was excluded in both cases by pleural biopsy. Involvement of other organs by IgG4-RD was the rule, especially thoracic lymphadenopathy which was prominent in all patients. In all cases, effusion responded to corticosteroids therapy. One patient developed radiological findings compatible with rounded atelectasis during remission. *Conclusions:* IgG4-RD may cause an ADA-positive, lymphocytic exudate with a high protein concentration, characteristics resembling tuberculous effusion. Thoracic lymphadenopathy, hyperglobulinemia, and an increased total IgG, IgG1, IgG4 may suggest the diagnosis. Not previously described, IgG4-RD pleural inflammation may result in rounded atelectasis. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 225-230)*

Key words: Immunoglobulin G4-related disease, IgG4-related disease, tuberculosis, ADA, pleural effusion, adenosine deaminase

Introduction

Immunoglobulin G4 related disease (IgG4-RD) is a systemic disorder with involvement of various organs. The condition is characterized by lymphoplasmacytic infiltration of single or multiple organs, resulting in mass lesions and/or organ dysfunction. Additional histological features include: storiform fibrosis and obliterative phlebitis, and abundance of IgG4-positive plasma cells in involved organs, often with elevated IgG4 serum levels [1-2]. Pulmonary manifestations of IgG4-RD may include involvement of the lung parenchyma, airways, vasculature, pleural spaces, and thoracic lymph nodes [1]. Pleural effusion is considered an uncommon manifestation of IgG4-RD, mainly mentioned in case reports.

Methods

We conducted a retrospective analysis of patients with a pleural effusion secondary to IgG4-RD who were treated in our clinic from January 2009 to December 2017. We assessed patients' clinical, radiographic, laboratory and pathological data, treatment and outcome. We included only cases with

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Correspondence: Dr. Ori Wand
Pulmonary Division, Meir Medical Center, 59 Tsernichowski St., Kfar-Sava, Israel, 4428164.
Tel: 972-97471556
ORCID ID: 0000-0002-7702-2967
Ori.wand@clalit.org.il

an established diagnosis of IgG4-RD (based on accepted criteria, including both the Boston pathologic criteria and the Japanese comprehensive and organ-specific criteria [2-3]), who had pleural effusions requiring evaluation or management with pleurocentesis. The study was approved by the Rabin Medical Center Institution Review Board (application No. RMC-0869-17) and in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines. Due to the retrospective nature of the study, a written informed consent was not required.

Results

We identified four patients with pleural effusion caused by IgG4-RD. All patients were males, mean age 74-years at time of diagnosis. One of the patients was a smoker with a history of chronic obstructive pulmonary disease (COPD). None of the patients had a history of other respiratory diseases, relevant occupational or environmental exposure, and none had known exposure to tuberculosis (TB). Human Immunodeficiency Virus (HIV) status was negative for all cases. All cases presented with dyspnea. Additional clinical and laboratory data are detailed in Table 1.

All patients had polycloncal hyperglobulinemia, with elevated serum concentrations of immunoglobulin G (IgG) and subclasses IgG4 and IgG1.

Radiographically, pleural effusions were bilateral in 3 cases and right-sided only in one case. Prominent enlargement of mediastinal and hilar lymph nodes was demonstrated in all patients. Two patients had additional parenchymal involvement in the form of diffuse ground glass opacities (GGO) consolidations.

Diagnosis of IgG4-RD was based on accepted criteria, including: organ involvement, elevated serum levels of IgG4, pathological features supporting the diagnosis and exclusion of other alternative diagnoses [2-3]. One patient had a prior diagnosis of IgG4-RD cholangitis and liver involvement supported by a liver biopsy. In the 3 other cases, pleural effusions were part of the initial presentation of IgG4-RD. Diagnosis of IgG4-RD was supported by a surgical pleural biopsy in case 2, by an excisional biopsy of a peripheral lymph node in case 4, and in cases 2 and 3 by a transbronchial biopsy. In case no. 3, transbronchial biopsies demonstrated a lymphoplasmacytic infiltrate with areas suggesting organizing pneumonia pattern, and abundant IgG4 positive cells. Thus, in all cases a diagnosis of definite or probable IgG4-Related respiratory disease was established [2-3].

Pleural effusions were exudates in all cases, with especially high protein concentrations and elevated concentrations of lactate dehydrogenase (LDH). There was a striking lymphocytic predominance in the cell counts, with no decrease in glucose and pH levels. In all cases bacterial and mycobacterial cultures were negative, and cytological evaluation was negative for malignancy.

Levels of adenosine deaminase (ADA) were measured in two patients and were elevated at 309 and 108 IU/L, respectively. In both cases TB was excluded by negative tissue cultures and histology of pleural biopsies specimens. In case no. 2, histological and immunohistochemical evaluation of the pleura fulfilled criteria for the diagnosis of definite IgG4-RD, specifically, a lymphoplasmacytic infiltrate with increased number of IgG and IgG4 positive cells was demonstrated in pleural biopsy specimens as well as in transbronchial biopsy specimens of the lung. In case no. 4 pleural biopsy demonstrated signs of non-specific chronic lymphocytic inflammation and a diagnosis of probable IgG4-RD was established by an excisional biopsy of an inguinal lymph node [2-3]. In both cases, Acid Fast stains and tissue cultures of the pleura were negative, and no granulomas were identified.

All four patients were treated with oral prednisone 0.5-1mg/kg daily as initial dose. All had good responses to steroid therapy with clinical improvement, as well as significant reduction in the size of pleural effusion and volume of lymph nodes, occurring within 4 weeks of therapy, and prednisone dosing was therefore gradually tapered down over several months. Patients no. 1 and 2 were able to stop prednisone completely after 9 and 7 months respectively. Patient 3 required ongoing immunosuppression, and azathioprine was added after 6 months of prednisone therapy, ultimately allowing complete steroid withdrawal. In case no. 4, steroid dose was quickly tapered down due to uncontrolled diabetes. His initial elevated level of ADA (108 IU/L) in the effusion was reduced (32 IU/L) with repeated therapeutic pleurocentesis. He was then treated with rituximab as a steroid sparing agent, with two doses of 1g given 14-days apart, resulting in long-term remission of his illness. However, follow-up computed tomography

Table 1. Data of patients with pleural effusion due to IgG4-RD

Case No.	**1**	**2**	**3**	**4**
Age	75	68	84	68
Sex	M	M	M	M
Serum studies (normal range)				
Globulins g/dL (2.0-3.5)	5.2	4	3.9	5.2
IgG mg/dL (700-1600)	4520	2491	2620	3030
IgG1 mg/dL (405-1011)	1967	NA	2010	1851
IgG4 mg/dL (3-201)	1170	NA	1420	297
Effusion studies (normal range in serum)				
Side	right	bilateral	bilateral	bilateral
White blood cells	NA	2900	2385	1326
Lymphocytes%	NA	96	88	85
LDH (effusion/serum) U/L (230-460) (ratio)	770/359 (2.15)	908/866 (1.05)	382/287 (1.33)	272/428 (0.64)
Protein (effusion/serum) g/dL (6.0-8.2) (ratio)	5.6/9.0 (0.62)	7.0/7.1 (0.99)	7.4/7 (1.06)	6.9/8.7 (0.79)
Glucose (effusion/serum) mg/dL (70-100) (ratio)	115/120 (0.96)	273/294 (0.93)	69/98 (0.70)	107/121 (0.88)
pH	7.30	7.39	7.34	7.41
ADA IU/L	NA	309	NA	108
Pleural biopsy				
Performed?	-	+	-	+
Diagnostic of IgG4-RD?	NA	+	NA	-
Level of diagnostic certainty for IgG4-RD	Established	Established	Established	Probable (Highly)
Histopathological confirmation for IgG4-RD derived from	Liver biopsy	Pleural and transbronchial biopsy	Transbronchial biopsy	Peripheral lymph node
Additional organ involvement by IgG4-RD	Liver and biliary, thoracic LNE	Lung parenchymal, thoracic LNE	Lung parenchymal, thoracic LNE	Generalized LNE
Response to steroid treatment	+	+	+	+

LNE – lymph nodes enlargement

6 months later demonstrated the development of rounded atelectasis in the right lung (Figure 1).

Discussion

Indeed, intrathoracic involvement in IgG4-RD is common, while pleural effusions are an unusual, yet a clinically significant manifestation [4-8]. In a prospective study by *Fei et al.*, intrathoracic lesions were identified in 87/248 cases with IgG4-RD, yet with pleural effusions in only 4 cases [8]. In a UK study by *Corcoran et al.*, 22/53 (42%) patients were categorized according to thoracic cross-sectional imaging studies as having thoracic involvement by IgG4-RD, yet only three patients had pleural effusions [9].

We have reviewed the literature for studies of large cohorts of patients with IgG4-RD (n > 20) and which report pulmonary or pleural involvement. We've identified 24 such studies from different countries, including a total of 1796 patients with IgG4-RD [8-9, 19-40]. The prevalence of pulmonary involvement in those series varied widely, from 3.6% to 59%, and was defendant on the study's design. Thus, the percentage of patients with pulmonary involvement was higher in studies in which CT of the chest was routine. The presence of pleural effusions was not

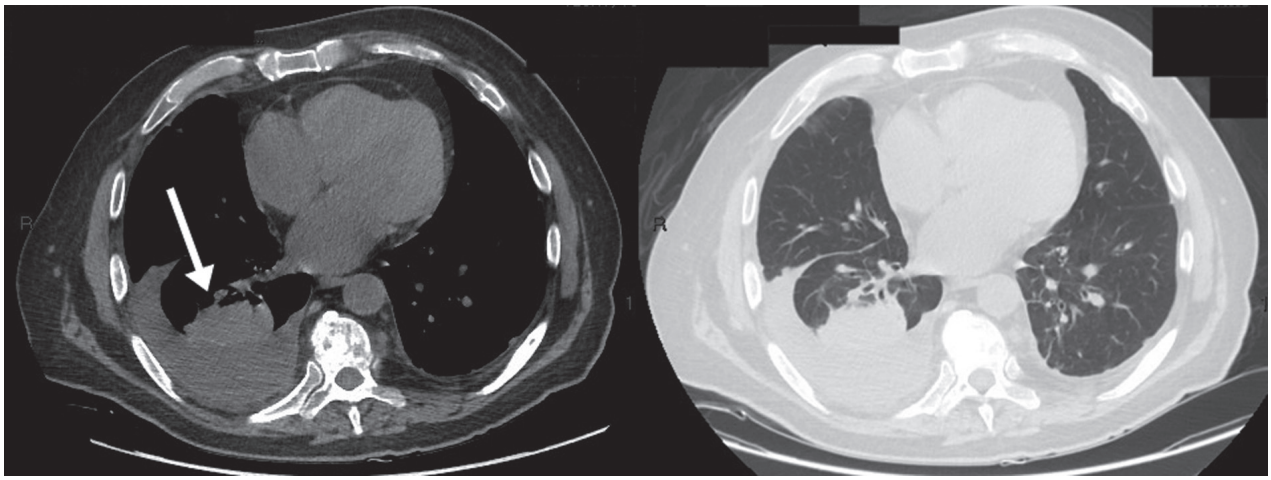

Fig. 1. Rounded atelectasis in a patient with IgG4-RD
CT of the chest from patient no. 4, demonstrating thickened pleura and a small effusion with signs of rounded atelectasis on the right (arrow).

addressed at all in six of the reviewed studies. From the remaining 18 studies which comprise 1228 patients, the prevalence of pleural effusions reached up to 5.7%, but was 0% in 14/18 studies. Thus, in the majority of large series of patients with IgG4-RD, no cases of pleural effusion were reported, while in a few studies they were very uncommon

Patients with IgG4-RD and pleural effusions have mostly been described in case reports. In addition to reporting two new cases, a literature review from 2016 also identified 13 previous case reports. In their review, 72% of patients were male with a mean age of 65, 55% had bilateral effusions and all cases had elevated serum levels of IgG4. In the majority (83%), additional organs involvement was described, mostly lungs, pericardium, and mediastinum. The authors suggest that serosal involvement by IgG4-RD, including pleural effusion, might be more common than previously considered [10]. This concurs to our experience, thus we agree that pleural effusions secondary to IgG4-RD are probably under-recognized and subsequently under-reported.

ADA, an enzyme involved in purine metabolism, catalyzes the deamination of adenosine to inosine and of deoxyadenosine to deoxyinosine. The enzyme is involved in the proliferation and differentiation of lymphocytes, specifically the T-lymphocytes. T-cells activation in the presence of live intracellular pathogens includes the release ADA, thus considered a marker of cell-mediated immune response [11]. Nonetheless, interpretation of ADA measurements in the evaluation of lymphocytic pleural effusions is complex. In endemic areas, positive results (> 35-40 IU/L) are highly sensitive and specific for tuberculosis (TB) and anti-tuberculous therapy is usually indicated [11]. Even in populations with a low incidence of TB, a positive ADA in a lymphocytic effusion, although very uncommon, still strongly suggests TB, while a negative result can exclude tuberculous pleural effusion [12]. In a large prospective study among 410 patients, pleural fluid ADA was elevated in only 7 (1.7%) patients with nontuberculous lymphocytic effusions [13]. Thus, an undiagnosed ADA-positive lymphocytic effusion in a low incidence population should prompt further evaluation including pleural biopsy. There are a few case reports of patients with IgG4-RD and an elevated pleural fluid ADA. A recent report from 2018 describes such a case and reviews 4 additional case reports [14].

In TB, stimulation of T cells by mycobacterial antigens results in increased ADA levels. However, the mechanisms associated with elevations of ADA levels in the pleural fluid of patients with IgG4-RD are unknown. In IgG4-RD, Th2-cell responses are predominantly activated at affected sites. While in contrast, in classic autoimmune conditions, the function of regulatory T-cells (Treg) cells is impaired. The mechanisms involved in IgG4-RD pathophysiology

are supported by large infiltrates of $CD4^+CD25^+$ Treg cells at affected sites [15]. Interestingly, similar to observations in TB patients [16], suggesting a possible common pathway of immune response inducing high ADA levels.

To the best of our knowledge, we describe the first case of rounded atelectasis solely attributed to IgG4-RD. In one other report, the patient had significant long-term occupational exposure to asbestos, resulting in stable round atelectasis for 8 years before the first symptoms of IgG4-RD emerged [17].

Many of the findings from our single center case series correlate with previous reports of cases with IgG4-RD pleural effusion. Most patients with IgG4-RD in general are elderly men, frequent clinical findings include elevated serum levels of IgG and IgG4 (in our series also of IgG1), and additional organ involvement of the disease, most commonly thoracic lymphadenopathy [18, 41]. Thus, our report adds significant information to the little data available regarding pleural effusions in IgG4-RD.

In summary, although uncommon, pleural effusion can be a manifestation of IgG4-RD, and even part of the initial presentation of the disease. IgG4-RD may cause an ADA-positive lymphocytic exudate, resembling tuberculous effusion. Clinicians should consider IgG4-RD in the differential diagnosis of an ADA-positive pleural effusion, which are very uncommon in areas with a low incidence of TB. In the absence of extra-thoracic involvement, clinical signs suggesting such diagnosis are mediastinal and hilar lymphadenopathy, polyclonal hyperglobulinemia, and elevated levels of IgG, IgG1 and IgG4. A pleural biopsy can aid in confirming the diagnosis. Pleural inflammation by IgG4-RD may also result in the development of rounded atelectasis.

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Rapidly non-IPF progressive fibrosing interstitial lung disease: a phenotype with an IPF-like behavior

Ngu Khine[1], Dalia Mudawi[1], Pilar Rivera-Ortega[1], Colm Leonard[1], Nazia Chaudhuri[1,2], George A. Margaritopoulos[1,2]

[1] ILD Unit, Manchester University Hospital NHS FT, Southmoore Road, Manchester M23 9LT, UK; [2] Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL, UK

Abstract. *Background:* A subgroup of patients with fibrotic ILD experience progression and several risk factors for ILD progression have been reported, such as male sex, older age, lower baseline pulmonary function, and a radiological or pathological pattern of usual interstitial pneumonia. *Objective:* To describe a possible new phenotype of rapidly non IPF progressive fibrosing with an IPF-like outcome. *Methods:* Three previously fit and well patients who developed a rapidly progressive ILD and died within 6 to 7 months from the initial development of respiratory symptoms. *Results:* Unlike what is currently known, our patients developed a severe fibrosing ILD with an IPF-like outcome despite a) being younger than the average patient with IPF, b) having received a non-IPF MDT diagnosis, c) having a non-UIP pattern on HRCT. Moreover and similarly to IPF, they failed to respond to immunosuppressive treatment which is the preferred treatment option in these cases. *Conclusion:* We believe that patients who present with similar characteristics should be considered as likely to develop a phenotype of rapidly progressive ILD and be treated with antifibrotic medications instead of immunosuppressive ones according to the favourable treatment response to antifibrotic therapy observed in clinical trials of patients with progressive fibrosing ILDs. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 231-233)*

Key words: Progressive, Fibrosis, IPF, ILD, UIP, NSIP

Progressive fibrosis is a characteristic of several interstitial lung diseases (ILD) that is strongly linked with mortality. Idiopathic pulmonary fibrosis (IPF) represents the prototype of inexorably progressive ILD [1]. Other fibrosing ILDs (idiopathic nonspecific interstitial pneumonia (NSIP), chronic fibrosing hypersensitivity pneumonitis, connective tissue disease (CTD)-associated ILD and unclassifiable fibrotic ILD) characterized histologically by a combination of inflammation and fibrosis can have an IPF-like behavior [2]. It was suggested that these subgroups of individual ILDs are amalgamated under the term of "progressive fibrosing ILDs" (PF-ILDs) [2]. However, there are unanswered questions regarding the a) diagnostic criteria [3], b) predictors of outcome [2] and c) appropriate treatment [4].

We present three cases of PF-ILD with striking clinical and possibly pathogenetic similarities (patients in their forties, ex/current smokers, unremarkable medical history, fully active prior to the development of respiratory symptoms which was triggered by respiratory infections, multidisciplinary diagnosis of rapidly non-IPF PF-ILD with IPF-like outcome). We believe that these cases may represent a specific phenotype of "rapidly" PF-ILD.

Case 1: A 49-years-old male, current smoker (pack-year:15) who worked in a warehouse presented

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Correspondence:George A. Margaritopoulos MD, PhD
ILD Unit, Manchester University Hospital NHS FT,
Wythenshawe Hospital, Southmoor Road,
Wythenshawe, Manchester M23 9LT, UK
georgios.margaritopoulos@mft.nhs.uk, gmargaritop@yahoo.gr

with a 3 months history of rapidly progressive breathlessness and cough triggered by a chest infection. At presentation, he used supplemental oxygen (3litres/minute at rest, 10litres/minute on ambulation). We identified possible occupational exposures. There was no evidence of CTD. The autoimmune screen was negative. The FEV_1 was 1.85 liters (55%), the FVC was 1.91 (46%), and the total lung capacity was 42%. A computed tomography (CT) pulmonary angiogram excluded pulmonary embolism and a high resolution (HR) CT showed a severe fibrotic ILD (NSIP pattern) with emphysema (Figure 1a). The echocardiogram showed a pulmonary artery systolic pressure of 52mmHg and right ventricular systolic dysfunction. He received intravenous and subsequently low-dose oral corticosteroids. Six weeks later, he presented with an acute exacerbation (AE) of ILD. The HRCT showed further progression (Figure 1b). He received intravenous antibiotics (CRP:15, negative cultures) and high dose oral steroids without any effect. He died 5 months after the development of significant symptoms.

Case 2: A 42-year-old male ex-smoker of one year (pack-year:15), bank clerk, referred with a 10 weeks history of progressive breathlessness developed after a chest infection which did not improve after several courses of antibiotics. At presentation, his exercise tolerance was 50 yards on the flat. The oxygen saturation at rest varied between 88%-92%. The bronchoalveolar lavage showed neutrophilia (35%) without microbial growth. The autoimmune screen was negative. There was no evidence of CTD and environmental exposures. The FEV_1 was 1.58L (39%), FVC was 1.7L (35%), the DL_{CO} was 38%. The HRCT showed an overlap between NSIP/organizing pneumonia [Figure 2a]. The echocardiogram was normal. His mother was under investigation for pulmonary fibrosis and his CT scan also showed evidence of liver cirrhosis raising the possibility of familial ILD. Genetic tests were not performed. Ambulatory oxygen was prescribed. He received oral prednisolone and 4 weeks later HRCT (Figure 2b) and lung function [FVC:1.38 (28%)] showed further progression. He received intravenous corticosteroids. Four weeks later, he presented with an AEILD. He was treated with high dose of oral corticosteroid and antibiotics (CRP:20, negative cultures). He died six months after the development of symptoms.

Case 3: A 43-year-old gentleman, ex-smoker of one year (pack-years: 25), book author, developed extreme fatigue, progressive breathlessness and cough associated with recurrent chest infections. At presentation he used supplemental oxygen (2litres/min at rest, 4litres/min on ambulation). The autoimmune screen was negative. Except from fatigue and non-specific joint pains, there was no clinical evidence of CTD. There were no environmental exposures. The HRCT showed a pattern of fibrotic NSIP with emphysema (Figure 3a). The echocardiogram was unremarkable. The FEV_1 was 2.8 L (74.5%), the FVC was 3.27 (71%), the DL_{CO} was 35%. He received intravenous and subsequently oral corticosteroids. Six weeks later, he described increased breathlessness although the oxygen requirements and lung function were stable. Mycophenolate Mofetil was added. Four weeks later he presented with an infective AEILD (CRP:110), increased oxygen requirements and a significant HRCT deterioration (Figure 3b). He received intravenous antibiotics. However, the oxygen requirements were further increased and he received again intravenous corticosteroids without any effect. He died 3 days later, 7 months after the development of respiratory and systemic symptoms.

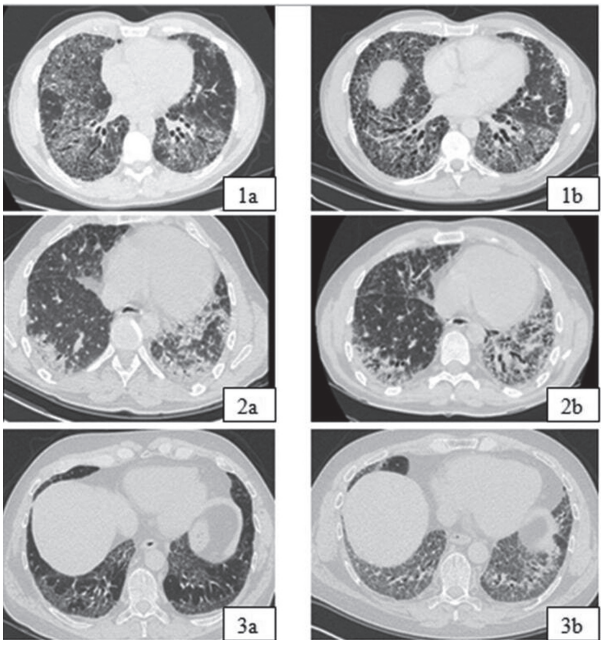

Fig. 1. HRCT at presentation (a) and at the time of AEILD (b).

Currently little is known about PF-ILD and most of the knowledge is extrapolated from studies on the prototype of PF-ILD, namely IPF. Our patients were younger than the average patient with IPF. We believe that, similarly to IPF clinical phenotypes [5], a phenotype of "rapid progressors" exists in non-IPF PF-ILDs. We observed that, unlike the majority of non-IPF PF-ILDs in which rapid progression is associated with the pattern of usual interstitial pneumonia (UIP) on HRCT [2], the "rapid progressor" phenotype can also present with a pattern of NSIP. Very few studies showed in the past that idiopathic NSIP can behave like IPF and our observation supports these findings [6-7]. We observed similarities between the non-IPF "rapid progressor" phenotype and IPF. Smoking, acute worsening of breathlessness, short-term disease progression and initiation of supplemental oxygen, common features in all three cases, predict mortality in IPF [8-11]. Our patients had a history of respiratory infections and it appears logical to hypothesize that immune defects and alteration of microbiome could be implicated in the pathogenesis and progression, similarly to IPF [12-13]. Another peculiarity is that the use of immunomodulation had a detrimental effect on survival. It is hoped that in non-IPF PF-ILDs the use of immunomodulation would stabilize or prevent progression given the hypothesis of fibrosis/inflammation co-existence [4]. We think that, despite the non-IPF diagnosis, immunomodulation may not be the ideal treatment in the context of PF-ILDs, in line with what was observed in IPF [14] and that antifibrotics may be a better choice given the results of recent trials [15-16].

We acknowledge that the absence of genetic tests represents a limitation of our study. It should be stressed however, that the performance of genetic tests has not been approved on a routine basis and most of the times funding is not available outside research projects. This is the reason for which, although a familial form has been suspected, genetic tests were not performed. We also acknowledge that the performance of bronchoalveolar lavage together with a transbronchial cryobiopsy would be significantly helpful for diagnostic and treatment purposes. However, the respiratory status of all patients both at presentation and during follow-up did not allow the performance of semi- or invasive procedures.

In summary, we present three cases of rapidly PF-ILDs which despite the absence of a definite/provisional diagnosis of IPF and of a UIP pattern on HRCT, had a typical IPF outcome. This is an almost unexplored field and large observational studies are warranted to better characterize the PF phenotype in terms of diagnosis and management.

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Treatment of newly diagnosed sarcoid-associated pulmonary hypertension with ambrisentan and tadalafil combination therapy

Eric Abston[1], Stephanie Hon[1], Romy Lawrence[2], Jeffrey Berman[3], Praveen Govender[1], Harrison W. Farber[4]

[1]Boston University Medical Center; [2]Brigham and Womens Hospital; [3]Boston University Medical Center; [4]Tufts Medical Center

Abstract. Sarcoid Associated Pulmonary Hypertension (SAPH) is a common complication of sarcoidosis and is associated with poor prognosis. SAPH can be due to multiple synergistic mechanisms and current therapeutic strategies treat systemic sarcoidosis and pulmonary hypertension separately. Several studies have been performed to develop an effective therapy for SAPH but have been met with mixed results. The AMBITION trial successfully treated incident patients with pulmonary arterial hypertension (PAH) with the upfront combination of ambrisentan and tadalafil; however combination therapy has not yet been studied in patients with SAPH. Here we report a cohort of patients with newly diagnosed SAPH who were treated with upfront combination therapy per the AMBITION study protocol. We report three subjects with newly diagnosed SAPH who were treated with combination ambrisentan and tadalafil. Baseline hemodynamics were compared with those from surveillance right heart catheterization while on therapy. Mean follow up period was 17 months. Each subject demonstrated clinical and hemodynamic improvement with combination therapy. This series is the first to evaluate upfront combination ambrisentan and tadalafil therapy for treatment of newly diagnosed SAPH. Despite the impressive clinical and hemodynamic improvement, the study is limited by its small size and retrospective nature. While these initial results are promising, further work is needed to fully evaluate this regimen for treatment of SAPH. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 234-238)*

Key words: Sarcoid associated pulmonary hypertension, sarcoidosis, pulmonary hypertension, Ambition Protocol, tadalafil, ambrisentan.

Introduction

Sarcoid Associated Pulmonary Hypertension (SAPH) is a well-known complication of sarcoidosis. SAPH is thought to develop as a result of complex interactions between sarcoid-associated inflammatory processes in both the lung parenchyma and the pulmonary vasculature. Mechanisms by which sarcoid disease can induce pulmonary hypertension include: hypoxia, pulmonary artery vasculitis, sarcoid associated heart failure, fibrotic destruction of pulmonary vasculature, occlusion of pulmonary vasculature by granulomatous tissue, and sarcoid-induced hepatic disease and subsequent portopulmonary hypertension[1]. Historically, SAPH has been difficult to study because any of these mechanisms can contribute to the development of SAPH[2]. While the epidemiology of SAPH has been the subject of several recent studies, its exact incidence remains unknown. In the largest cohorts of patients with known sarcoidosis who were screened for Pulmonary Hypertension (PH) by echocardiography SAPH was observed in 3-50%[3, 4, 5, 6]. In studies using right heart catheterization, 49-73% of patients with known sarcoidosis were diagnosed with SAPH[7, 8]. This broad range is likely due, in part to the heterogeneity of the sarcoid population and

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Correspondence: Eric Abston
Pulmonary Center
715 Albany St
Boston, MA 02118

the varying severity of the underlying sarcoidosis. Yet, the presence of SAPH confers a poorer prognosis compared to sarcoidosis alone[3, 9, 10, 11].

Treatment of SAPH has focused on optimizing treatment of the underlying sarcoidosis and management of the PH as distinct issues. Studies specifically evaluating the effect of treating the sarcoidosis with immunomodulatory therapy have demonstrated mixed results on pulmonary hemodynamics[10, 12, 13, 14]. Use of pulmonary vasodilators approved for treatment of Pulmonary Arterial Hypertension (PAH) in patients with SAPH has been hampered by a lack of robust studies evaluating such treatment in this population. What is known is based on small studies[15]. For example, prostanoids have been effective vasodilators in SAPH[16, 17] whether administered by the inhaled or intravenous route[18, 19, 20]. In addition, endothelin receptor antagonists (bosentan) and phosphodiesterase-5 inhibitors (sildenafil) have improved SAPH in some patients[21, 22, 23]

The benefits of upfront combination therapy have recently been established in patients with newly diagnosed group 1 PH (PAH); AMBITION was the first randomized controlled trial to demonstrate improvement in outcomes with the upfront combination of ambrisentan and tadalafil in the treatment of newly diagnosed PAH[24]. Previously, ambrisentan mono-therapy had demonstrated improvement in exercise capacity and hemodynamics in patients with PAH. Likewise, tadalafil, as either monotherapy or add on therapy, also improved hemodynamics, six minute walk test, and time to clinical worsening[25, 26]. In patients with SAPH treatment with either of these agents as monotherapy has led to variable results. Ambrisentan monotherapy did demonstrate improvement in functional class in one study[27]. Likewise, tadalafil monotherapy has demonstrated equivocal results in this patients population[28]. However, there are no studies that have evaluated combination therapy in patients with newly diagnosed SAPH.

In the current report, we describe a series of newly diagnosed SAPH patients treated with the upfront combination of ambrisentan and tadalafil (AMBITION protocol)[24].

Design and Data Collection

We conducted a retrospective review of all patients with SAPH and identified those treated with the combination of ambrisentan and tadalafil (AMBITION protocol) in accordance with a protocol approved by the Boston University Institutional Review Board. For each case, we collected patient demographics, stage of sarcoidosis, treatment for sarcoidosis, pulmonary function testing, echocardiography, baseline and post-treatment hemodynamics, complications of therapy, and clinical outcome.

The diagnosis of sarcoidosis was confirmed by review of the medical record, including compatible historical information and/or pathology findings. Patients were classified as having SAPH if they had a mean pulmonary arterial pressure (mPAP) > 25 mm Hg (Patients were diagnosed and treated under the previous PH guidelines and not under the currently proposed definition[24, 29]) by right heart catheterization (RHC) with PAOP < 15 mmHg and PVR > 3 WU. None of the patients included in this report, had evidence of any of the following: connective tissue disease, portal hypertension, congenital or valvular heart disease, HIV infection, history of anorexigen or methamphetamine use, or thromboembolic disease.

Treatment Protocol

Patients were treated in accordance with the AMBITION trial protocol. Daily ambrisentan and tadalafil were initiated following diagnostic RHC with goal of 10 mg and 40 mg daily, respectively. Dose adjustments were made as dictated by patient symptoms and clinical status. Patients were treated with supplemental oxygen as required to maintain oxygen saturation ≥90%. Patients underwent surveillance RHC to assess response to treatment as clinically indicated.

Because of its small size, this series was not powered for statistical analysis.

Results

This case series contains 3 subjects with newly diagnosed SAPH who were treated with the AMBITION protocol, with a mean follow-up of 17 months. All subjects tolerated full dose ambrisentan and tadalafil with no significant side effects. Surveillance right heart catheterization (mean interval 12 months) demonstrated improvement in hemodynamics in each patient: mPAP 40 ± 10 baseline vs 24 ± 5 mmHg post treatment, CO 3.8 ± 1.9 baseline vs 7 ± 2 L/min post treatment, PVR 12.6 ± 12.4 baseline vs 2.4 ± 0.8 WU post treatment. In addition to hemodynamic

improvement, there was also improvement in NYHA functional class from FC III at baseline to FC II post treatment and 6 minute walk distance from 305 ± 58m baseline to 427 ± 86m post treatment.

Case Descriptions:

Patient 1 is a Caucasian male with history of hypertension and distant smoking history. He was diagnosed with lung biopsy proven Scadding stage 4 sarcoidosis at age 44. He was initially managed with steroids, but two years later transitioned to hydroxychloroquine and minocycline because of disease progression. Seven years later, because of further progression, minocycline was stopped and methotrexate started with improvement in symptoms. He later developed a spontaneous pneumothorax with persistent air leak, ultimately treated by lobectomy.

At age 56, because of progressive DOE, hypoxia, and decline in lung function, he was evaluated for pulmonary hypertension; right heart catheterization demonstrated SAPH. Tadalafil and ambrisentan were started per AMBITION protocol. There were no side effects with tadalafil, but ambrisentan caused fluid retention that responded to diuretics. This treatment resulted in improved symptoms, exercise tolerance and hemodynamics. Eighteen months later he again noted progressive DOE, worsening hypoxia, and diminished exercise tolerance. Imaging demonstrated progressive fibrotic lung disease and surveillance right heart catheterization demonstrated worsening hemodynamics. Because of these findings, he eventually underwent bilateral lung transplant and is currently alive and well.

Patient 2 is a 74 year old female with history of spinal stenosis, hypothyroidism, and Scadding stage 4 sarcoidosis. Initially diagnosed at age 63 because of uveitis and arthralgia, she later developed hypercalcemia, chronic lymphopenia, and palpitations associated with recurrent supraventricular tachycardia. Sarcoidosis was diagnosed by mediastinal biopsy. She was initially treated with prednisone for two years prior to initiation of methotrexate as a steroid sparing agent. She was stable on this regimen for ~8 years; then developed worsening pulmonary disease and was transitioned to infliximab.

Because of progressive dyspnea, limiting activities of daily living, and worsening hypoxia, despite stable lung disease, she underwent right heart catheterization that demonstrated severe SAPH. She was treated with tadalafil and ambrisentan per the AMBITION protocol without side effects. With this regimen, she had dramatic improvement in symptoms, clinical status and hemodynamics. Unfortunately, twelve months later, she died from urosepsis.

Patient 3 is a 56 year old male, with history of hypertension, severe obstructive sleep apnea treated with BiPAP, type 2 diabetes, distant 33 pack/year smoking history, and Scadding stage 4 sarcoidosis. He was diagnosed with sarcoidosis in 2004 by transbronchial biopsy and treated with prednisone for several years. The sarcoidosis was difficult to control despite multiple regimens, including methotrexate, azathioprine, and infliximab; it was eventually controlled with a combination of methotrexate, adalimumab, and doxycycline.

Because of progressive dyspnea and stable lung disease, he underwent right heart catheterization that demonstrated SAPH. He was treated with tadalafil and ambrisentan per AMBITION protocol without side effects and with improvement in symptoms, clinical status, and hemodynamics. With advancing fibrotic lung disease his symptoms have again progressed and he is awaiting lung transplantation.

Discussion

In the current series of patients with biopsy proven sarcoidosis subsequently diagnosed with SAPH by right heart catheterization, we report the initial experience with upfront treatment with ambrisentan and tadalafil per the AMBITION protocol. Despite previous studies showing equivocal response to ambrisentan and tadalafil as monotherapy in patients with SAPH, these three patients responded to combination therapy with improvement in clinical status, functional class and hemodynamics. Moreover, this regimen was well-tolerated with minimal side effects.

The prospect that patients with newly diagnosed SAPH might receive significant benefit from upfront combination therapy is potentially important. The initial response to therapy seen in this small series is highly encouraging, especially since patients with a significant burden of fibrotic disease (Scadding stage 4) tend to respond poorly to vasodilator therapy. Clearly, additional studies are warranted to

investigate the effects of combination therapy in a larger cohort of patients with SAPH.

While it is difficult to generalize the results from three patients, two (patients 1 and 3) had a significant response to therapy initially, but later had progression of symptoms which was attributed to worsening fibrotic lung disease. This does suggest that combination therapy might not have long-term durability in patients suffering from progressive fibrotic disease and that these patients should be closely monitored for clinical worsening. However, the initial and extended improvement suggests that combination therapy might: 1) provide symptomatic relief and/or improvement in these patients; 2) allow time for more aggressive treatment of the advancing fibrosis; and/or 3) allow more time to evaluate the patient for lung transplantation and/or possibly delay the need for it.

The current study is limited by its small size, retrospective nature, and lack of randomization. Moreover, it was not adequately powered to detect statistically significant treatment effect changes. Conclusions: We report a cohort of three patients with biopsy proven sarcoidosis subsequently diagnosed with SAPH by right heart catheterization. Each patient was treated with an upfront combination of tadalafil and ambrisentan in accordance with the AMBITION protocol. All patients demonstrated marked improvement in hemodynamics, symptoms, and 6-minute walk distance. Although these initial results are encouraging, especially since all patients had Scadding stage 4 disease, additional studies are needed to evaluate the effect of combination therapy in patients with SAPH.

Table 2: Hemodynamics at initial diagnosis (Baseline) and after treatment (mean followup catheterization 12 months). Hemodynamic measurements were obtained by right heart catheterization at baseline (diagnosis of SAPH) and during treatment

Table 1: Patient Characteristics

	Patient 1	**Patient 2**	**Patient 3**
Age	57	73	57
Sex	Male	Female	Male
Race	Caucasian	Caucasian	Caucasian
BMI	23.4	21.8	30.1
Scadding Stage	4	4	4
Sarcoid Treatment	Methotrexate	Infliximab	Combination
Pulmonary Function Tests			
FVC L (% Pred)	2.7 (59)	1.52 (49)	2.63 (57)
FEV1 L (%Pred)	1.49 (43)	0.61 (26)	1.58 (45)
FEV1/FVC	55	40	60
DLCO mL/mmHg/min (% Pred)	10.5 (44)	4.85 (23)	11.4 (44)
Echocardiogram			
EF (%)	60	73	58
PASP (mmHg)	47	72	NA
Right Ventricle Size	Normal	Normal	Normal
Right Ventricle Hypertrophy	No	Yes	Yes

Table 2. Patient Hemodynamics and Functional Capacity

	Baseline				**Treatment**			
	Patient 1	**Patient 2**	**Patient 3**	**Avg**	**Patient 1**	**Patient 2**	**Patient 3**	**Avg**
RV sys (mmHg)	49	58	41	49 ± 9	36	38	38	37 ± 1
RA dia (mmHg)	1	5	3	3 ± 2	0	0	0	0 ± 0
PAP sys (mmHg)	54	62	40	52 ± 11	40	40	39	40 ± 1
PAP dia (mmHg)	31	31	23	28 ± 5	23	13	6	14 ± 9
mPAP (mmHg)	40	50	31	40 ± 10	29	23	20	24 ± 5
PCWP (mmHg)	4	7	13	8 ± 5	11	5	6	7 ± 3
CO Fick (L/min)	4.84	1.61	4.86	3.8 ± 1.9	5.53	8.23	8.5	7 ± 2
CI Fick (L/min/m^2)	2.48	1.96	2.29	2.2 ± 0.3	2.97	4.9	4.04	4 ± 1
PVR Fick (WU)	7.4	26.7	3.7	12.6 ± 12.4	3.2	2.3	1.7	2.4 ± 0.8
NYHA FC	2	2	2	2	3	3	3	3
6 Min walk (M)	365	250	300	305 ± 58	450	500	332	427 ± 86

with tadalafil and ambrisentan (Treatment). RV (right ventricle), PAP (pulmonary artery pressure), mPAP (mean PAP), PCWP (pulmonary capillary wedge pressure), CO Fick (cardiac output via Fick's principle, CI cardiac index), PVR (pulmonary vascular resistance), NHYA FC (New York Heart Association Functional Class). mPAP improved from 40 ± 10 mmHg to 24 ± 5 mmHg, CI improved from 2.2 ± 0.3 to 4.0 ± 1.0 L/min/m2. The study was not powered for statistical analysis.

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Pulmonary hypertension secondary to takayasu's arteritis: management using a combined medical and interventional approach

Matthew Nitzberg[1], *Raj Parikh*[2], *Praveen Govender*[2], *Harrison W. Farber*[3]

[1]Pulmonary Critical Care Medicine, Newton-Wellesley Hospital, Newton, MA; [2]The Pulmonary Center, Boston University School of Medicine, Boston, MA; [3] Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center, Boston, MA

Key words: Takayasu's Arteritis (TA), Pulmonary Hypertension, Pulmonary Arterial Hypertension, Epoprostenol, Endovascular Stent

To the editor:

Takayasu's Arteritis (TA) is a chronic, large-vessel vasculitis that typically occurs in women between the ages of 10 and 40.[1] Glucocorticoids, steroid-sparing immunosuppressive agents, and biologics are commonly used for the medical management of TA; however, large-vessel stenoses may require stenting or bypass procedures.[2] The pulmonary artery (PA) network is affected in up to 50% of TA cases, which may result in severe pulmonary hypertension (PH) due to PA stenoses.[3] Successful cases of PA stenting have been reported; however, none has reported the use of a combination of medical and interventional therapies nor documented the long term effects of PA stenting on cardiopulmonary hemodynamics measured by right-heart catheterization (RHC).[4]

We present a 48-year-old female who presented with 3 years of progressive shortness of breath and exertional chest pain. Her past medical history was significant for Takayasu's arteritis diagnosed at the age of 27 by angiogram revealing left subclavian artery stenosis. She had previously been treated with prednisone 40mg and transitioned to methotrexate for 10 years, resulting in clinical remission. At that point, all medications were discontinued; she was lost to follow-up until occurrence of respiratory symptoms.

At the time of presentation, she had World Health Organization (WHO) Functional Class (FC) IIIb symptoms and an exam significant for asymmetric blood pressures between her upper extremities, resting pulse oximetry of 94% which decreased to 88% with ambulation, and a loud S2 with grade III holosystolic murmur at the right sternal border. There was no clubbing, peripheral edema, jugular venous distention, or crackles on lung examination. Echocardiogram revealed moderate right ventricular dilation, severe right atrial dilation, 3+ tricuspid regurgitation, and an estimated PA systolic pressure of 167 mmHg; ejection fraction estimated at 70%. RHC confirmed severe PH (PA systolic: 150 mmHg, PA diastolic: 41 mmHg, mean PA pressure: 65 mmHg, pulmonary vascular resistance: 1219 dynes•s/cm5; pulmonary capillary wedge pressure: 17 mmHg; cardiac index: 1.85 L/min). Computer tomography pulmonary angiogram revealed diffuse narrowing of the right PA, focal stenosis of the left PA with distal aneurysmal dilatation, and no pulmonary emboli (Figure 1). Erythrocyte sedimentation rate was normal. The patient was initiated on

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Correspondence: Raj Parikh
The Pulmonary Center
Boston University School of Medicine,
72 East Concord Street, R-304
Boston, MA 02118
Raj.parikh@bmc.org

continuous epoprostenol through a tunneled central catheter; it was gradually uptitrated to 34 ng/kg/min over a 10-month period with clinical improvement. Repeat RHC at 10 months revealed improvement in hemodynamics (Table 1); however, at 34 months, she presented with worsening peripheral edema, and hemodynamic findings of RV dysfunction (Table 1). Pulmonary arteriogram demonstrated an 8 cm 80% stenosis of the right main PA with an elevated trans-stenotic pressure gradient (peak 90 mmHg, mean 42 mmHg); there were no hemodynamically significant stenosis of the left PA. The patient was reluctant to undergo an interventional procedure and thus, medical management was intensified. Epoprostenol was uptitrated to 52 ng/kg/min.

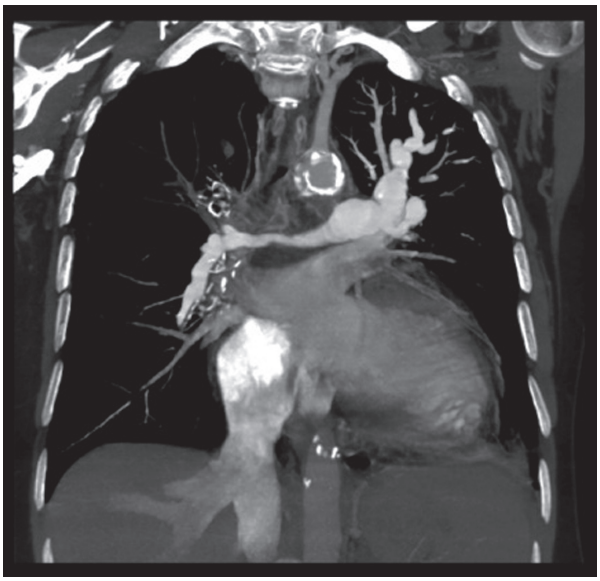

Fig. 1.

Despite 4 years of medical therapy, right heart failure progressed and the patient developed ascites, required frequent hospitalizations, and deteriorated to FC IV. At this point, the patient agreed to stenting and two overlapping balloon expandable stents were deployed in the right main PA. The peak trans-stenotic gradient deceased from 82 mmHg to 35 mmHg after deployment of the stents. Post-procedure course was complicated by pulmonary edema of the right lung due to the rapid increase in perfusion to the chronically hypo-perfused tissue; however, this responded effectively to furosemide and a short course of inhaled nitric oxide. The patient also received 500mg of intravenous methylprednisolone one day prior to and for three days after the procedure, followed by a 2-week prednisone taper to mitigate a procedure-related arteritis flare. Epoprostenol was continued at 52 ng/kg/min. One week after stent placement, renal function and liver function tests normalized, oxygen requirements decreased, and she improved to FC III. Four years after stent placement, she remained on Epoprostenol and had improved to FC II, no longer requiring supplemental oxygen. RHC demonstrated markedly improved hemodynamics and cardiac function. The PA stent was patent and free-flowing (Figure 2).

This is an interesting case of TA induced PA stenosis and severe PH treated with a combination of Epoprostenol and PA stenting. With Epoprostenol,

Table 1. Major diagnostic and therapeutic interventions

Event	RHC 1 and Epo initiation	RHC 2	RHC 3	PA stent placement	RHC 4
Time since epo initiation (months)	0	10	34	49	114
Epo Dose (ng/kg/min)	0	34	52	52	36
CVP (mmHg)	12	8	15	n/a	9
PAP (mmHg)	150/41	135/18	120/24	n/a	94/17
Mean PAP (mmHg)	65	59	58	n/a	46
PCWP (mmHg)	17	14	20	n/a	13
CI (L/min)	1.85	2.3	1.80	n/a	2.91
PVR dyn•sec/cm5	1219	983	1012	n/a	530

Epo – epoprostenol; RHC – Right Hearth Catheterization; PA – Pulmonary Artery; CVP – central venous pressure; PAP – pulmonary artery pressure; PCWP – pulmonary capillary wedge pressure; CI – cardiac index; PVR – pulmonary vascular resistance

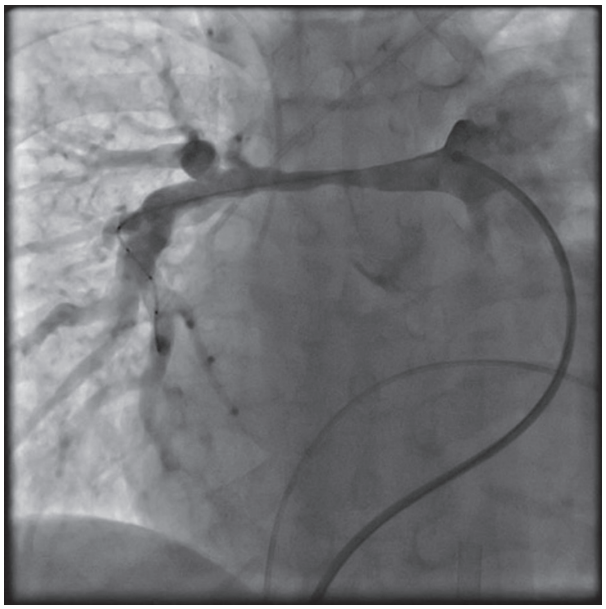

Fig. 2.

the patient survived 4 years to stent placement. For patients who have a contraindication to PA stenting, or who do not wish to undergo the procedure, pulmonary vasodilator therapy may be an option albeit there have been no studies evaluating efficacy and safety of vasodilator therapy in this entity. Given the rarity of TA-associated PH, it is unlikely a placebo-controlled study would be feasible. This case is the first to report long-term hemodynamic follow-up after stenting for PA stenosis from TA. The RHC information, in this case, provides objective support for use of PA stenting in TA-associated PH by demonstrating marked and sustained hemodynamic improvement over a 5-year period. The one prior case series of PA stenosis from TA showed good clinical outcomes with stenting.[4] In this series, 3 of 4 patients underwent stenting of the stenosis and had sustained clinical response and maintained lower pulmonary pressures by image-based surrogate measurements. The one patient who underwent only balloon angioplasty developed recurrence of symptoms at 18 months. All of the patients in this series remained on prednisone at the end of their follow-up periods and the authors suggest corticosteroid maintenance to prevent re-stenosis. Our patient only used corticosteroids for a brief peri-procedural period and had no evidence of re-stenosis on angiogram 4 years after stenting.

PA stenting is an effective treatment in the management of selected patients with TA-induced PA stenosis. In TA-associated PH, pulmonary vasodilators, such as Epoprostenol, may be effective since this entity is a form of connective tissue disease related PH. Further studies are needed to support these conclusions.

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Subcutaneous sarcoidosis: a report of 13 cases and its association with extracutaneous sarcoidosis

Toshiyuki Yamamoto
Department of Dermatology, Fukushima Medical University, Fukushima, Japan

Key word: skin, subcutaneous, spontaneous regression

Introduction

Sarcoidosis is a systemic granulomatous disorder, mainly involving the lung, eye, and skin. Cutaneous sarcoidosis accounts for 20-35% of sarcoidosis patients, with different ratios depending on race (1-3). Cutaneous manifestations of sarcoidosis exhibit specific and non-specific lesions. Specific lesions histologically show non-caseating epithelioid cell granulomas, and the clinical features include papules, nodules, plaques, scars, lupus pernio, as well as various rare forms such as erythema nodosum-like, psoriasiform, ulcerative, and ichthyosiform lesions (3,4). By contrast, a representative of the non-specific lesions, which lack sarcoidal granulomas histologically, is erythema nodosum. Subcutaneous sarcoidosis is one of a rare form of cutaneous sarcoidosis, and studies with large study populations are few (5-8). Herein, we report 13 cases of subcutaneous sarcoidosis which we experienced in our department over a period of ten years.

Materials and methods

The current study was approved by the institutional review board of Fukushima Medical University. All enrolled patients were diagnosed with cutaneous sarcoidosis based on histological findings of non-caseating epithelioid cell granulomas, using the pathology database of the Department of Dermatology at Fukushima Medical University, between 2010 and 2019. Other granulomatous diseases, such as tuberculosis, deep fungal infection, necrobiosis lipoidica, or granuloma annulare, were excluded. Clinical charts were retrospectively examined and the patients' data such as age, gender, types of cutaneous lesion, serum levels of angiotensin converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R), extracutaneous organ involvement, and clinical course were evaluated.

Results

Thirteen cases (3 males and 10 females) developed subcutaneous sarcoidosis, involving the upper extremities (n = 4), trunk (n = 5), and lower extremities (n = 9) (Figure 1). The age range was 28-74 years old, and the mean age was 58.0 ± 15.1 years. A single lesion was observed in two cases, whereas multiple lesions were present in the other 11 cases. The other types of cutaneous sarcoidosis the patients had were scar sarcoidosis (n = 3), erythema nodosum-like lesion (n = 3), plaque-type (n = 3), lupus pernio (n = 1), and ichthyosiform sarcoidosis (n = 2). Histologically, sarcoidal granulomas were densely located in the subcutaneous tissues (Figure 2). Subcutaneous sarcoidosis developed as an initial manifestation in six cases. The lung was involved in all cases, and

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Correspondence: Toshiyuki Yamamoto, M.D., Ph.D.
Department of Dermatology, Fukushima Medical University, Fukushima 960-1295, Japan
E-mail: toyamade@fmu.ac.jp

eye sarcoidosis was observed in seven cases. Cardiac sarcoidosis was observed in one case only, and facial palsy was observed in two cases. The other systemic diseases they had were ulcerative colitis (n = 1) and Cushing syndrome (n = 1). Serum levels of ACE were elevated in eight cases (61.5%) (25.4 to 66.2 IU/L, normal; 7-25), and sIL-2R was increased in six cases among eight cases examined (937 to 2730 U/ml, normal; 121-613) (unknown five cases). Regression was observed in seven cases, whereas two cases were resistant to therapies. Follow-up period was less than 1 year in three cases, and one case was not followed. Among the seven cases with resolution, oral prednisolone was used only in one case. Patients' characteristics were summarized in Table 1.

Discussion and conclusions

Subcutaneous sarcoidosis was previously estimated to account for 1.4-6% of the patients with systemic sarcoidosis (9,10); however, recent studies have shown that subcutaneous sarcoidosis was observed in 11.8% of specific cutaneous sarcoidosis cases (5), suggesting that the reported incidence of subcutaneous sarcoidosis may have been underestimated.

To date, there have been some reports on subcutaneous sarcoidosis. Ahmed et al. reported that, in their 21 cases of subcutaneous sarcoidosis, there was a female predominance and frequent involvement of extremities (upper extremity in 21 cases and lower extremity in 16 cases) (6). Other types of cutaneous lesion were observed in 15 cases (71%), which showed plaques (n = 6), papules (n = 4), erythema nodosum (n = 4) and scar sarcoid (n = 1). Systemic evaluation was performed on 20 patients, among whom pulmonary involvement was most common (n = 16), followed by arthritis (n = 3), mucositis (n = 3), peripheral neuropathy (n = 2), kidney sarcoid (n = 2), and uveitis (n = 2). Another study on subcutaneous sarcoidosis from Japan reported on nine patients with subcutaneous sarcoidosis among 35 patients with cutaneous sarcoidosis (7). Among the nine patients, eight were female. The involved sites were the upper extremities (n = 2), lower extremities (n = 7), trunk (n = 1) and hip (n = 1).

In the present study, during the years between 2010 and 2019, 57 cases of cutaneous sarcoidosis were diagnosed in our hospital, among which subcutaneous sarcoidosis was observed in 13 cases (22.8 %). Previous reviews suggest that subcutaneous sarcoidosis is a rare form of cutaneous sarcoidosis (8);

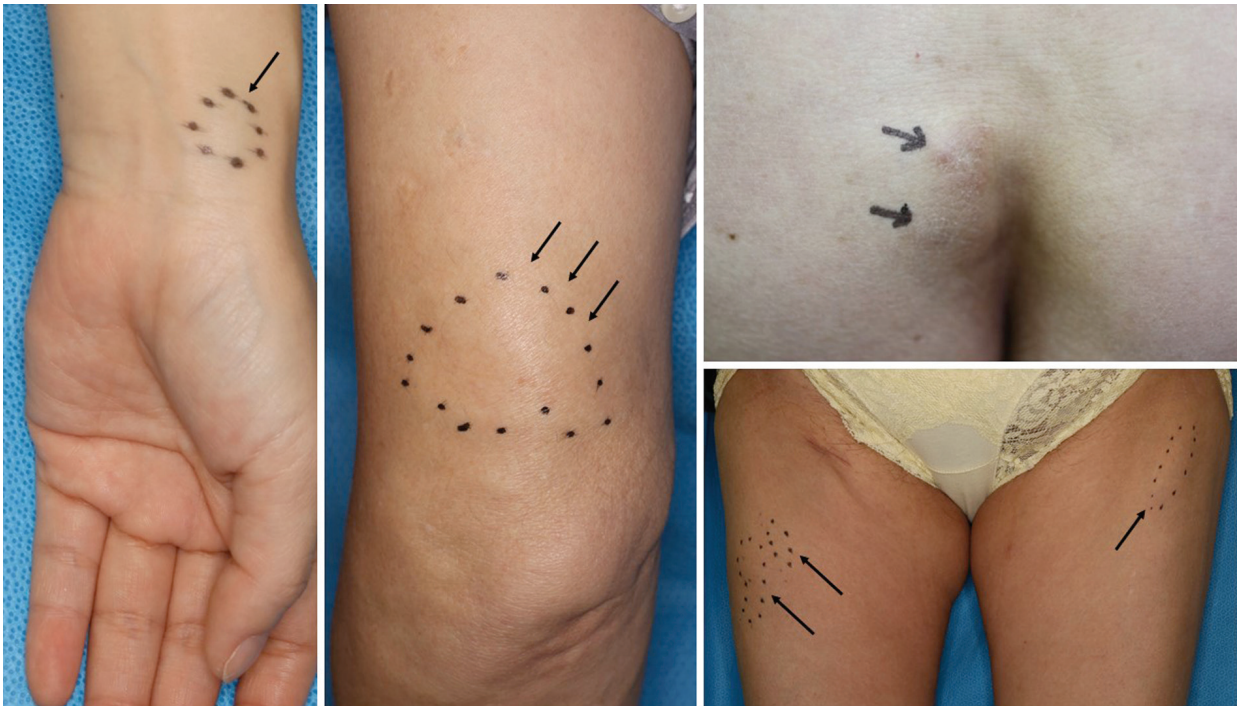

Fig. 1. Clinical features of subcutaneous nodules involving the upper and lower extremities, and buttock (indicated by arrows).

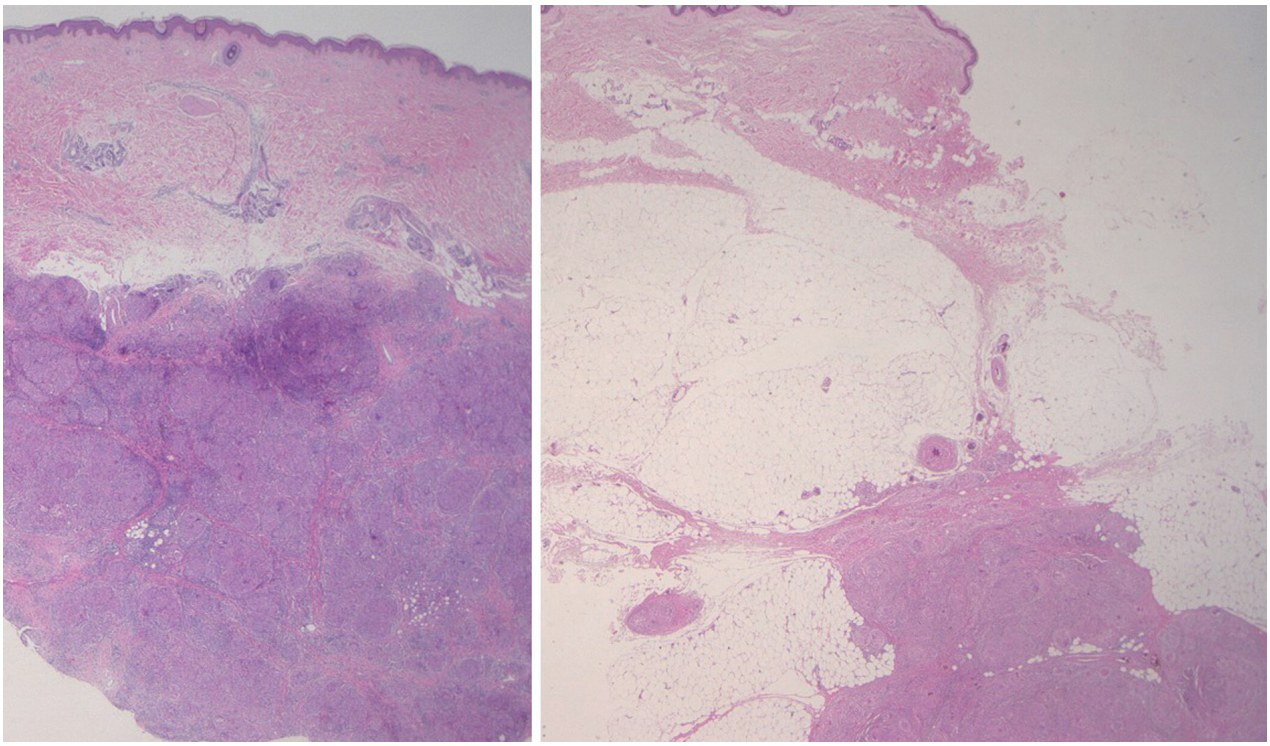

Fig. 2. Histological features showing epithelioid granulomas in the subcutis.

Table 1.

Case	Age/Sex	Location of subcutaneous nodule	Other types of cutaneous sarcoid	Lung	Eye	Heart	ACE	sIL2R
1	28/F	Lower extremity	Scar sarcoid	+	-	-	20.6	n.d.
2	69/M	Lower extremity	-	+	+	+	12	571
3	46/F	Trunk	Scar sarcoid, Erythema nodosum-like, Ichthyosiform	+	+	-	56.8	962
4	52/F	Lower extremity	Plaque	+	+	-	66.2	2730
5	39/F	Forearm, Abdomen	Erythema nodosum-like, Lupus pernio	+	+	-	20.6	1430
6	74/F	Buttock	Erythema nodosum-like	+	-	-	42.2	n.d.
7	73/F	Lower extremity	Scar sarcoid, Plaque	+	+	-	44	2140
8	63/F	Forearm	-	+	+	-	42.5	n.d.
9	65/M	Lower extremity	Plaque	+	-	-	19.6	n.d.
10	70/M	Upper/lower extremity, chest	-	+	-	-	16.8	565
11	69/F	Thigh	-	+	-	-	27.1	n.d.
12	41/F	Lower extremity, forearm, buttock	-	+	-	-	38.2	937
13	65/F	Lower extremity	Scar sarcoid, Ichthyosiform	+	+	-	25.4	1350

Table 2.

	Patient No.	F:M	Age distribution (mean)	Location	Lung(n)	Eye(n)	Heart(n)	Spontaneous regression
Marcoval J, et al. (2005)	10	9:1	29-70 (53 y.o.)	Upper extremity (10) Lower extremity (5)	9	Unknown	Unknown	6
Ahmed I, et.al. (2006)	21	15:6	26-61 (46.3 y.o.)	Upper extremity (21) Lower extremity (16) Trunk(6)	16	2	0	12
Ando M, et al.	9	8:1	23-69 (55.5 y.o.)	Upper extremity (2) Lower extremity (7) Trunk(2)	9	4	0	3
Present study	13	10:3	28-74 (58.0 y.o.)	Upper extremity (4) Lower extremity (9) Trunk(5)	13	7	1	7

however, subcutaneous sarcoidosis may not be so rare as was previously considered. In consistent with the previous data, our results showed a female predominance in Japanese patients, and the lower extremities were most commonly involved. Nearly half of the patients (6/13: 46.1%) in the current study developed subcutaneous lesions as an initial manifestation, which was similar to the results of a previous study (5). Pulmonary sarcoidosis was observed in all cases, and ophthalmological involvement was observed in over 50%. By contrast, cardiac involvement was rare, and peripheral neuronal involvement (Heerfordt syndrome) was observed in two cases. Regression was observed in seven of the 13 cases (53.8 %) in our series, for which systemic corticosteroid was administered in only one case, which suggests that subcutaneous sarcoidosis may be expected to resolve spontaneously. Other reports have shown that regression was observed with a ratio of 33.3-60% (5-8).

A comparison of previous reports is shown in Table 2. Subcutaneous sarcoidosis is closely associated with systemic involvement especially pulmonary sarcoidosis (5,7,8). In conclusion, subcutaneous sarcoidosis is a specific form of cutaneous sarcoidosis that is sometimes observed in Japanese patients with a female predominance, involving the lower leg, and frequently accompanies lung and ocular sarcoidosis. The present study has a few limitations, such as retrospective study and a lack of a long-term follow-up period. Nevertheless, our results may indicate a different frequency of cutaneous types of sarcoidosis patients in Japan compared to other countries.

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